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REVIEW-SYMPOSIUM

# Fructose catalysis and its metabolic effects: Exploring host–microbiota interactions and the impact of ethnicity

Florine H.M. Westerbeke, Melany Rios-Morales, Ilias Attaye and Max Nieuwdorp

*Department of Internal and Experimental Vascular Medicine, Amsterdam University Medical Centers, Amsterdam, The Netherlands*

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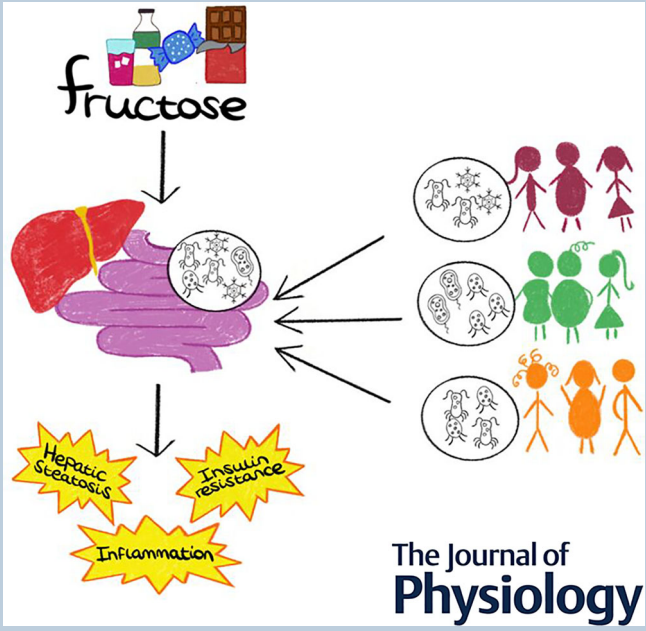


**Abstract figure legend** This graphical abstract is a schematic representation highlighting the interactions between dietary fructose, gut microbiota and ethnicity in shaping metabolic health.

**Florine H.M. Westerbeke** is a medical doctor and PhD candidate in the department of vascular medicine at the Amsterdam University Medical Centers. After 1 year of clinical experience in internal medicine, she started her PhD in the research group of Professor Max Nieuwdorp. Her research focuses on the role of the gut microbiota in metabolic syndrome and type 2 diabetes, with particular interest in fructose catabolism. By investigating the complex interactions between diet, gut microbiota and individual metabolic responses, the team aims to provide comprehensive new insights that will support the development of microbiota-targeted interventions and personalized nutrition strategies for improved metabolic health.



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**Abstract** Important health disparities are observed in the prevalence of obesity and associated non-communicable diseases (NCDs), including type 2 diabetes (T2D) and metabolic dysfunction–associated steatotic liver disease (MASLD) among ethnic groups. Yet, the underlying factors accounting for these disparities remain poorly understood. Fructose has been widely proposed as a potential mediator of these NCDs, given that hepatic fructose catabolism can result in deleterious metabolic effects, including insulin resistance and hepatic steatosis. Moreover, the fermentation of fructose by the gut microbiota can produce metabolites such as ethanol and acetate, both which serve as potential substrates for *de novo* lipogenesis (DNL) and could therefore contribute to the development of these metabolic conditions. Significant inter-ethnic differences in gut microbiota composition have been observed. Moreover, fructose consumption varies across ethnic groups, and fructose intake has been demonstrated to significantly alter gut microbiota composition, which can influence its fermenting properties and metabolic effects. Therefore, ethnic differences in gut microbiota composition, which may be influenced by variations in fructose consumption, could contribute to the observed health disparities. This review provides an overview of the complex interactions between host and microbial fructose catabolism, the role of ethnicity in shaping these metabolic processes and their impact on host health. Understanding these interactions could provide insights into the mechanisms driving ethnic health disparities to improve personalized nutrition strategies.

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**Corresponding author** F. H.M. Westerbeke, Department of Internal and Experimental Vascular Medicine, Amsterdam University Medical Centers, Location AMC, Amsterdam, The Netherlands. Email: f.h.m.westerbeke@amsterdamumc.nl

**Key points**

- Dietary fructose consumption has increased substantially over recent decades, which has been associated with the rising prevalence of obesity and non-communicable diseases (NCDs) such as type 2 diabetes and metabolic dysfunction-associated steatotic liver disease.
- Pronounced disparities among different ethnic groups in NCD prevalence and dietary fructose consumption underscore the need to elucidate the underlying mechanisms of fructose catabolism and its health effects.
- Together with the well-known toxic effects of hepatic fructose catabolism, emerging evidence highlights a role for the small intestinal microbiota in fermenting sugars like fructose into various bacterial products with potential deleterious metabolic effects.
- There are significant ethnic differences in gut microbiota composition that, combined with varying fructose consumption, could mediate the observed health disparities.
- To comprehensively understand the role of the gut microbiota in mediating fructose-induced adverse metabolic effects, future research should focus on the small intestinal microbiota.
- Future research on fructose – microbiota – host interactions should account for ethnic differences in dietary habits and microbial composition to elucidate the potential role of the gut microbiota in driving the mentioned health disparities.

## Introduction

Dietary fructose consumption has significantly increased over the past few decades due to the extensive use of sucrose (table sugar) and high-fructose corn syrup (HFCS) in processed foods and sugar-sweetened beverages (SSBs). Among adolescents and adults in the United States, dietary fructose consumption increased from 37 to 54.7 g/day between 1977–1978 and 2008 (Vos et al., 2008). This represents 10.2% of the daily caloric intake. In contrast to glucose, fructose is metabolized in a distinctive manner which has been linked to adverse metabolic dysregulations, including the development of insulin resistance and hepatic steatosis (Jung et al., 2022; Lim et al., 2010; Tappy, 2021; Tappy & Lê, 2010). Increased dietary fructose consumption has been

proposed as an important mediator of the increasing incidence of obesity, type 2 diabetes (T2D), metabolic dysfunction–associated steatotic liver disease (MASLD) and other non-communicable diseases (NCDs) (Bray et al., 2004; Johnson et al., 2007; Jung et al., 2022; Lim et al., 2010; Tappy & Lê, 2010).

The ongoing pandemic of obesity, T2D and other NCDs represents a significant health and economic burden. As reported by the World Health Organization (WHO), in 2021, 7 of the 10 leading causes of mortality worldwide were NCDs, accounting for 38% of all deaths (WHO, 2021). This underscores the urgent need for the development of novel preventive and therapeutic strategies. However, there are discrepancies in the prevalence of these diseases among ethnic groups, even within the same geographical area (prevention CfDCa, 2024; de Wilde et al., 2018; Hales CM, 2020; Meeks et al., 2016). These health disparities are already evident among children, as demonstrated by a study conducted on children aged 2–15 years living in the Netherlands (de Wilde et al., 2018). In 2015 the prevalence of obesity was highest among South Asian children (21.5%), whereas Turkish (7.6%), Moroccan (4.5%) and Dutch (1.5%) children exhibited significantly lower rates. The prevalence of obesity among US adults between 2017 and 2018 was highest among non-Hispanic Black individuals (49.6%), followed by Hispanic (44.8%), non-Hispanic White (42.2%) and non-Hispanic Asian adults (17.5%) (Hales CM, 2020). Furthermore, between 2017 and 2020 the estimated prevalence of diabetes in US individuals showed notable disparities across ethnic groups, with rates ranging from 13.6% among non-Hispanic Whites to 17.4% among non-Hispanic Black individuals (prevention CfDCa, 2024). Similarly the prevalence of T2D among ethnic minorities in Europe was demonstrated to be significantly higher when compared to Europeans. Migrants from South Asian origin exhibited the highest rate, with an odds ratio (OR) of 3.7 (Meeks et al., 2016). However the underlying factors causing this difference in disease burden among ethnicities are not completely understood (Agyemang et al., 2021).

The latter may be partially attributed to variations in gut microbiota composition and function, which is increasingly recognized as a crucial contributor to metabolic health. In the context of the human 'microbiota', the term encompasses all living organisms that coexist with their host, including bacteria, algae, archaea, fungi and small protists (Berg et al., 2020). The human microbiota predominantly colonizes the gastrointestinal tract. Here, the diversity and abundance of bacterial species increase along the tract, reaching a concentration of $\sim 10^{12}$ colony-forming units per millilitre in the colon (Kastl et al., 2020). The gut microbiota plays a pivotal role in the breakdown of certain nutrients, with the degradation of complex carbohydrates and the formation of short-chain fatty acids being well established (Oliphant & Allen-Vercoe, 2019; Rowland et al., 2018). Moreover, recent research has indicated that the gut microbiota also plays a substantial role in the metabolism of simple carbohydrates (Ruigrok et al., 2021; Zoetendal et al., 2012). In particular, these recent findings indicate that the small intestinal microbiota (SIM) is highly important in the metabolism of sugars, including fructose.

The significant differences in the gut microbiota composition observed among individuals from different ethnic backgrounds (Brooks et al., 2018; Deschasaux et al., 2018; Dwiyanto et al., 2021), coupled with the microbiota's crucial role in nutrient metabolism, indicate that fructose catabolism may vary across ethnic groups. These variations could influence the metabolic effects of fructose and potentially contribute to the observed health disparities among individuals from different ethnic backgrounds.

In this review we aim to provide a comprehensive overview of the current understanding of fructose host and microbial catabolism, the associated metabolic dysregulations and their subsequent health effects. We will particularly explore the influence of ethnicity on these processes and its potential contribution to health disparities.

**Trends and ethnic variations in dietary fructose consumption.** Since its introduction in the 1970s, HFCS has become a main source of added sugar (Parker et al., 2011; White, 2014). Typically containing 55% fructose and 45% glucose, HFCS is almost similar in composition to sucrose, which is 50% fructose and 50% glucose. However HFCS has several advantages compared to sucrose. These include its relatively low cost, its liquid form which makes it more soluble and easier to use than crystalline sucrose and its ability to retain moisture, thereby improving the shelf life of products (Parker et al., 2011; White, 2014). This has led to the widespread use of HFCS in processed foods, particularly SSBs, which has contributed to the observed increase in dietary fructose intake. As awareness of the adverse effects of fructose consumption has increased, there has been a decline in added sugar consumption in recent years (DiFrancesco et al., 2022; Rogers et al., 2024). However, added sugars still account for a significant proportion of total caloric intake, remaining above the WHO's recommended limit of 5% of total energy intake (WHO, 2015).

It is important to note, however, that general numbers on fructose and sugar consumption do not account for variations among different racial and ethnic groups. Several studies have identified ethnic variations in the intake of added sugars and SSBs, which are significant sources of fructose. Between 2017 and 2020 added sugar intake among US non-Hispanic White, non-Hispanic

Black and Hispanic adults was 63.8, 71.8 and 59.6 g/day, respectively (Liu & Mozaffarian, 2024). The percentage of US adults consuming any SSB on a given day in 2017–2018 was 65.3% for non-Hispanic White, 77.9% for non-Hispanic Black and 77.8% for Hispanic individuals (Dai et al., 2021). Furthermore the estimated daily caloric intake from sugary drinks among US children aged 10–13 years was reported, with the lowest rates observed among Asian (118.5 calories) and White (139.7 calories) children (Boehm et al., 2022). Similar to the rates noted in adults, the estimated caloric intake from sugary drinks was found to be the highest among Black and Hispanic children, with 238.9 and 283.3 calories per day, respectively. Moreover, significant ethnic variation in daily SSB consumption was reported in a multiethnic Dutch cohort, with Moroccan adults reporting the highest rates and Dutch individuals reporting the lowest rates (Balvers et al., 2024). These results indicate that higher consumption of added sugars, which include fructose, is predominantly observed among Black and Hispanic individuals, whereas lower intake is generally seen among individuals of White and Asian descent.

## Fructose catabolism by the host

*Fructose absorption.* Dietary fructose is passively absorbed across the apical membrane of the small intestine by glucose transporter 5 (GLUT5) and across the basolateral membrane by glucose transporter 2 (GLUT2) (Burant et al., 1992; Cheeseman, 1993; Kane et al., 1997; Mueckler & Thorens, 2013). Its apical transport is distinct from that of glucose, which is primarily facilitated by the active sodium-dependent glucose co-transporter 1 (SGLT1). SGLT1 transports glucose with a high affinity and low capacity (Hediger & Rhoads, 1994; Wright et al., 2011). However, at high luminal glucose concentrations, there is apical recruitment of GLUT2 (Kellett, 2001; Kellett & Brot-Laroche, 2005), which mediates diffusive glucose absorption with low affinity and high capacity (Mueckler & Thorens, 2013; Uldry et al., 2002). Compared to the fast and (almost) complete absorption of glucose, fructose absorption is relatively slow and its capacity is limited (Sun & Empie, 2012), which indicates why fructose malabsorption seems to be a common phenomenon. One study has indicated that 53% of healthy participants showed malabsorption of an oral fructose dose of 25 g and 73% had fructose malabsorption after a 50 g oral fructose dose (Beyer et al., 2005). A review of fructose malabsorption rates in healthy individuals reported malabsorption of an oral fructose dose of 50 g in 38%–81% of the individuals and malabsorption of 25 g of oral fructose in 11%–50% (Gibson et al., 2007). These results indicate that excessive fructose consumption results in incomplete intestinal absorption and subsequent overflow of fructose to the distal small intestine and colon, which can then influence gut microbiota composition and function. Although intestinal fructose absorption is limited, fructose feeding in rats has been shown to induce an increased expression of intestinal GLUT5 to maximally enhance luminal fructose uptake (Burant & Saxena, 1994; David et al., 1995; Shu et al., 1997). GLUT5 mRNA and protein levels were similarly elevated in the intestine of diabetic individuals, enhancing fructose absorption (Dyer et al., 2002). Ras-related protein in brain 11a (Rab11a) is crucial for GLUT5 trafficking to the apical membrane of the small intestine (Sobajima et al., 2014). Consequently, Rab11a would play an important role in the enhancement of luminal fructose uptake in response to high luminal fructose levels.

*Hepatic fructose catabolism and associated metabolic effects.* After fructose uptake in the intestine, hepatic fructose catabolism causes various adverse metabolic effects that can contribute to the development of insulin resistance and hepatic steatosis (Fig. 1). Hepatic fructose catabolism is initiated by the phosphorylation of fructose to fructose-1-phosphate (F1P), catalysed by ketohexokinase (KHK) (Heinz et al., 1968). F1P is then cleaved to dihydroxyacetone phosphate and glyceraldehyde-3-phosphate by aldolase B. This pathway differs from glucose catabolism, in that it allows fructose to bypass the main rate-limiting step of glycolysis, leading to unregulated fructose catabolism (Tappy & Lê, 2010). This results in a depletion of ATP and an excessive production of acetyl-CoA, a precursor for fatty acid synthesis, through pyruvate oxidation (Lim et al., 2010; van den Berghe et al., 1977). Moreover, when excessive levels of acetyl-CoA are produced, the metabolic capacity of the tricarboxylic acid (TCA) cycle is exceeded, resulting in the accumulation of citrate which serves as a potential substrate for *de novo* lipogenesis (DNL) (Lim et al., 2010). In this process acetyl-CoA is converted to malonyl-CoA, which inhibits mitochondrial $\beta$-oxidation, consequently contributing to intrahepatic lipid accumulation (Lim et al., 2010). The depletion of ATP and the subsequent formation of AMP result in a decline in intracellular ATP and phosphate levels, stimulating the degradation of AMP to inosine monophosphate and, consequently, increased uric acid production (Bode et al., 1973; van den Berghe et al., 1977). Increased plasma uric acid levels can induce mitochondrial oxidative stress, which in turn inhibits aconitase in the TCA cycle, leading to citrate accumulation (Lanaspa et al., 2012). The accumulation of citrate then stimulates the activation of the lipogenic enzymes ATP-citrate lyase (ACL) and fatty-acid synthase (FAS) leading to fatty acid and triglyceride formation (Lanaspa et al., 2012). Furthermore, hepatic fructose catabolism activates the transcription factors sterol regulatory element binding protein 1c (SREBP-1c)

and carbohydrate response element binding protein (ChREBP), which also augment the expression of ACL, FAS and other lipogenic enzymes, thereby further enhancing DNL (Koo et al., 2009; Nagai et al., 2002; Uyeda & Repa, 2006).

In addition to its impact on DNL and hepatic steatosis, hepatic fructose catabolism has been linked to the development of hepatic insulin resistance (Aeberli et al., 2012; Softic et al., 2017; Stanhope et al., 2009; ter Horst et al., 2016). The mechanisms underlying fructose-induced hepatic insulin resistance are multifaceted. During fructose-induced DNL there is an increased synthesis of intermediate metabolites, including diacylglycerols (DAGs). DAGs activate the novel protein kinase C epsilon, which impairs insulin receptor substrate 1 (IRS-1) activity through serine phosphorylation, thereby leading to hepatic insulin resistance (Boden et al., 2005; Samuel et al., 2010; Softic et al., 2020). Fructose-induced uric acid production can stimulate NADPH oxidase, producing reactive oxygen species (ROS) (Sautin et al., 2007). Furthermore uric acid can lead to mitochondrial dysfunction, increasing mitochondrial ROS production and inducing mitochondrial oxidative stress (Federico et al., 2021; Lanaspa et al., 2012). Mitochondrial ROS production can contribute to endoplasmic reticulum (ER) stress and vice versa (Jegatheesan & De Bandt, 2017; Lim et al., 2009). Increased free fatty acids (FFA), as well as the described uric acid–induced mitochondrial oxidative stress and ER stress, can activate inflammatory pathways, leading to the production of inflammatory cytokines (Federico et al., 2021). More fructose-induced uric acid production can directly induce inflammation by activating the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome (Braga et al., 2017). Inflammatory cytokines such as tumor necrosis factor alpha (TNF-$\alpha$) and interleukin-6 (IL-6), as well as the induced oxidative stress and ER stress, can all activate c-Jun-N-terminal kinase (JNK) and inhibitor of nuclear factor kappa-$\beta$ (IKK$\beta$) (Lim et al., 2009; Xie et al., 2021). Increased activity of JNK and IKK$\beta$ also promotes serine phosphorylation of IRS proteins, thereby contributing to the development of hepatic insulin resistance (Aguirre et al., 2002; Chen et al., 2015; Gao et al., 2002; Hirosumi et al., 2002; Wei & Pagliassotti, 2004; Wei et al., 2005).

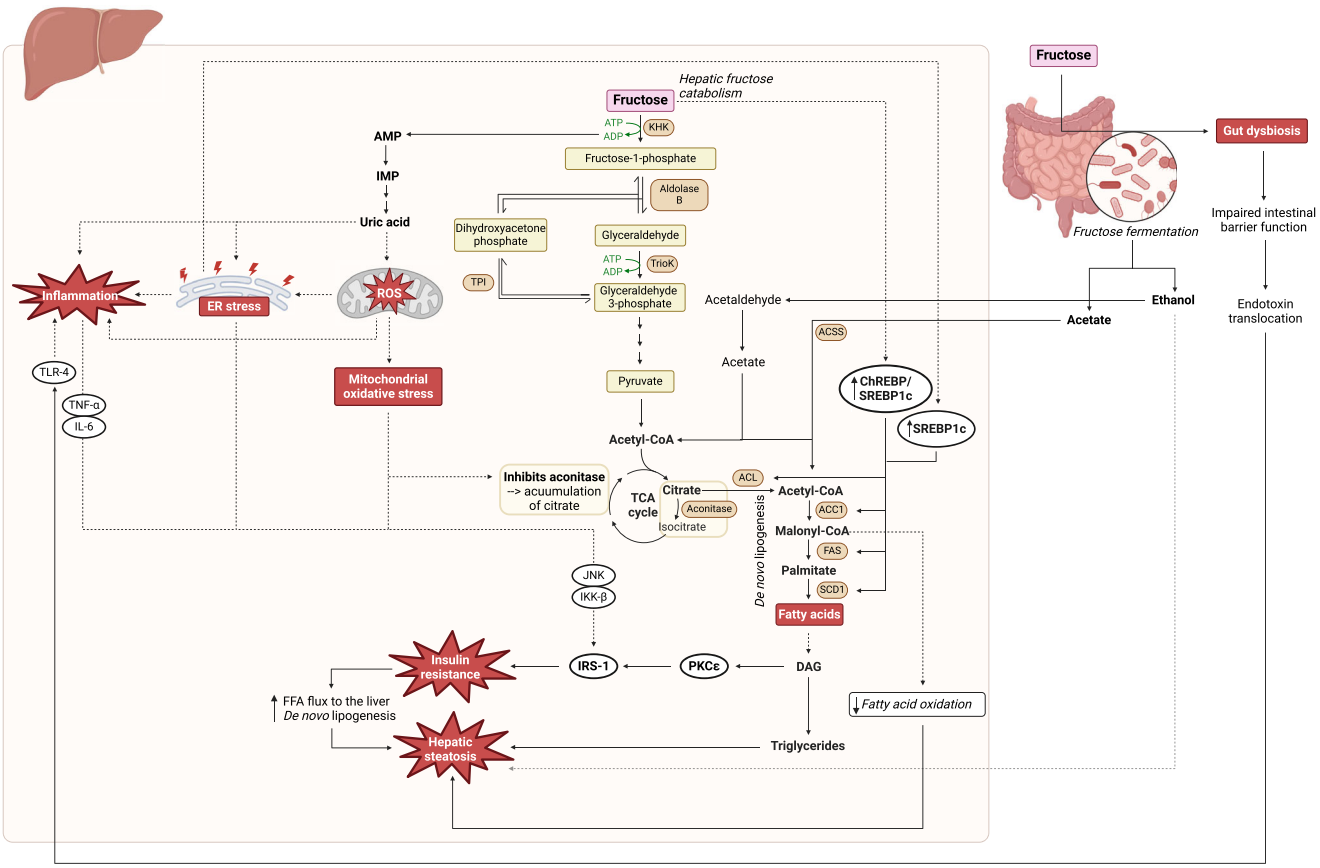


**Figure 1. Metabolic effects of hepatic fructose catabolism and fructose fermentation**
This figure provides an overview of the metabolic effects induced by hepatic fructose catabolism and fructose fermentation. It illustrates the complexity of fructose-induced metabolic effects which contribute to the development of insulin resistance and hepatic steatosis.

In conclusion, an increased dietary intake of fructose can lead to various metabolic dysregulations, which promote the development of hepatic steatosis and insulin resistance, both of which are hallmarks in the development of NCDs. In the condition of insulin resistance, there is impaired inhibition of lipolysis, which consequently increases FFA flux to the liver (Carpentier, 2021; Choi et al., 2010; Marchesini et al., 2001). Moreover, insulin resistance stimulates hepatic DNL (Nogueira & Cusi, 2024; Smith et al., 2020; Utzschneider & Kahn, 2006). Thus, the development of insulin resistance can further enhance the development of hepatic steatosis. This indicates that fructose contributes to a vicious cycle in which various metabolic disturbances reinforce one another, thereby promoting deleterious effects on host health.

*Fructose catabolism: A role for the small intestine?* Although the liver has traditionally been considered the primary site of fructose catabolism, recent findings by Jang et al. (2018) have definitely changed our perspective of this metabolic process. In their study in mice they demonstrated that physiological doses of fructose are primarily metabolized in the small intestine, where fructose is converted to glucose and organic acids before entering the portal circulation. Expression of the enzyme glucose-6-phosphatase (G6Pase), which produces glucose by dephosphorylating glucose-6-phosphate, has previously been detected in the human small intestine (Rajas et al., 1999), suggesting a gluconeogenic potential. Furthermore, fructose administration led to a marked increase in the expression of *G6pc* (catalytic subunit of G6Pase) and *Glut5* genes in the small intestine of mice, with both showing more than a 20-fold upregulation (Jang et al., 2018). In addition to these genes, fructose administration significantly increased the expression of fructose 1,6-biphosphatase (*Fbp1*), aldolase B and triose kinase (*Tkfc*) in the small intestine, all of which are involved in fructose catabolism (Jang et al., 2018). In wild-type mice, fructose feeding induced the intestinal mRNA and protein expression of fructolytic and gluconeogenic enzymes (Patel et al., 2015). However, the fructose-induced upregulation of these enzymes was impaired in GLUT5-, KHK- and Rab11a knock-out mice. This suggests that increased fructose uptake and metabolization are crucial for the regulation of intestinal fructolytic and gluconeogenic enzymes (Patel et al., 2015).

Thus, the small intestine reduces the passage of fructose to the liver, protecting it from fructose-induced hepatic steatosis and insulin resistance (Jang et al., 2020). Nevertheless, Jang et al. demonstrated that at high fructose levels (>1 g/kg), fructose clearance and absorption by the small intestine become saturated, resulting in fructose overflow to the liver and more distal parts of the intestine. This opens up new targets for fructose catabolism not only by the host but also by the gut microbiota, as fructose becomes available for gut microbial fermentation in the distal small intestine and colon.

### Intestinal fructose catabolism and the gut microbiota: Is there a link?

*Sugar fermentation by SIM.* As the small intestine can efficiently absorb dietary derived sugars, particularly glucose, sugars are not a primary substrate for the gut microbiota under regular conditions. Therefore, sugar fermentation is underexplored when compared to (indigestible) complex carbohydrate fermentation. However, as previously described, fructose absorption can be saturated at high fructose doses making it available for gut microbial fermentation (Jang et al., 2018). Moreover, Zoetendal et al. demonstrated that the SIM is predominantly influenced by the capacity of its microbial constituents to metabolize sugars, suggesting an important role for the SIM in sugar fermentation (Zoetendal et al., 2012). A significant enrichment of multiple phosphotransferase systems (PTS), which are used by bacteria for the uptake and phosphorylation of sugars, was observed in the small intestinal metagenome when compared to faecal metagenomes (Zoetendal et al., 2012). Furthermore, there was significant enrichment of genes encoding pathways related to sugar degradation and fermentation within the small intestine, including the pentose phosphate pathway and fermentation pathways, such as lactate and propionate fermentation (Ruigrok et al., 2021; Zoetendal et al., 2012). PTS and these central metabolic pathways were also overrepresented in the metatranscriptome of the small intestine, once more highlighting a pivotal role of the SIM in sugar uptake and catabolism (Zoetendal et al., 2012). In particular, a majority of PTS transcripts were expressed by *Streptococci*, indicating that *Streptococci* are the predominant users of the available sugars within the small intestine (Zoetendal et al., 2012). Additionally, Yilmaz et al. used ileostoma contents to detect changes in carbon sources and metabolites between fasted and fed states (Yilmaz et al., 2022). Notably, there were no postprandial changes in mono- and disaccharide levels, suggesting complete uptake of non-absorbed sugars by the SIM. Collectively, these results indicate that the SIM is of significant importance in the catabolism of sugars. Nevertheless, the challenging accessibility of the small intestine has thus far constrained a comprehensive investigation into the SIM and sugar catabolism. More research is warranted to further identify key microbial species and elucidate the metabolic pathways involved *in vivo*.

*Fructose fermentation and host effects.* The gut microbiota can metabolize or ferment diet-derived sugars through a variety of pathways. The glycolytic

Embden–Meyerhof–Parnas, Entner–Doudoroff and pentose phosphate pathways are used to metabolize sugars into pyruvate as a primary end product (Wolfe Alan, 2015). Although glucose is the primary substrate, other hexoses and pentoses can also enter these glycolytic pathways. In the case of fructose, prior conversion to a phosphorylated form of either fructose or glucose is required. The pyruvate yielded by these glycolytic pathways can be fermented by the gut microbiota through various fermentation pathways, producing a diverse range of metabolites. The specific metabolites formed are dependent on the pathway employed and the potential for cross-feeding among bacteria. Lactic acid fermentation is an important fermentation pathway utilized by lactic acid bacteria (LAB), which are particularly abundant in the small intestine (Leite et al., 2020). Some LAB possess the enzyme phosphoketolase, enabling them to perform heterolactic fermentation. In this pathway sugars, including fructose, enter the glycolytic pentose phosphate pathway, followed by the phosphoketolase pathway (Pessione, 2012; Wang et al., 2021; Wolfe Alan, 2015). The end products of heterolactic fermentation include lactate, ethanol or acetate and $CO_2$. Heterolactic bacteria are primarily found within the family Leuconostocaceae, including the genera *Leuconostoc*, *Weisella* and *Oenococcus* and some *Lactobacillus* species (Pessione, 2012; Wang et al., 2021; Wolfe Alan, 2015).

Gut microbiota–derived acetate and ethanol from fructose fermentation can exert deleterious effects on the host. Microbial acetate can be activated into acetyl-CoA in both the cytosol and the mitochondria, unlike acetyl-CoA derived from the host's fructose catabolism, which is produced only in the mitochondria (Fig. 1). Cytosolic acetyl-CoA can serve as an important precursor for fatty acid synthesis, promoting DNL. Mitochondrially produced acetyl-CoA is converted into citrate, which can be transported to the cytosol and converted back to acetyl-CoA to be involved fatty acid synthesis (Moffett et al., 2020). However, the amount of citrate that exits the mitochondria depends on the availability of mitochondrial acetyl-CoA (depending on the nutritional state) and the tissue's energy demands, which may require full oxidation of citrate (Moffett et al., 2020). In mice, it has been shown that microbial acetate (and its cytosolic activation) plays a big role in hepatic lipogenesis (Zhao et al., 2020a). Notably, there is also literature on the signalling effect of acetate and its role in activating $\beta$-oxidation activation (den Besten et al., 2015). Similar to the previous discussion this will largely depend on the availability of the acetate pool, which, in the case of excessive fructose intake, is expected to overwhelm cellular processes. Furthermore, ethanol can be metabolized into acetaldehyde and subsequently converted to acetate, therefore also serving as a potential substrate for DNL. In addition to this pathway, ethanol has a significant impact on numerous aspects of lipid metabolism, promoting lipid accumulation and contributing to the development of hepatic steatosis and insulin resistance (Lustig, 2013; You & Arteel, 2019). Not unsurprisingly, increased endogenous ethanol production by the gut microbiota has been associated with the development of MASLD ametabolic dysfunction-associated steatohepatitis (MASH) (Meijnikman et al., 2022; Yuan et al., 2019; Zhu et al., 2013).

In addition to the described ethanol production through heterolactic fermentation, gut microbiota can produce ethanol from sugar fermentation through additional pathways such as mixed acid fermentation. This process yields multiple end products, including ethanol, lactate, acetate, succinate, formate and gases, and is intestinal pH dependent. Mixed acid fermentation is carried out by bacteria belonging to the Enterobacteriaceae family, in particular *Escherichia coli* (Ciani et al., 2008; Ward, 2015). The Enterobacteriaceae family constitutes a small fraction of the healthy human gut microbiota (Moreira de Gouveia et al., 2024). Although they are typically more abundant in the colon, they also represent a substantial portion of the less-dense microbial population in the small intestine (Yersin & Vonaesch 2024; Leite et al., 2020).

A recent systematic review by Mbaye et al. identified 85 ethanol-producing microbes in humans, including both fungi and bacteria (Mbaye et al., 2024). The most represented bacterial family was Enterobacteriaceae, predominantly comprising *E. coli and Klebsiella pneumoniae* species, in addition to other identified bacterial species belonging to the Lachnospiraceae and Clostridiaceae families and the Lactobacillales order. In humans some *K. pneumoniae* strains were previously associated with high endogenous alcohol production (Yuan et al., 2019). Fructose could be a substrate for ethanol production, but evidence is limited on ethanol-producing microbiota on fructose in particular. One article described significant ethanol production from fructose fermentation in *Weisella confusa*, a species belonging to the group of LAB (Elshaghabee et al., 2016). Another article demonstrated excessive endogenous ethanol production by three *Klebsiella* species in fructose-fed mice (Xue et al., 2023).

These data therefore indicate that fructose fermentation, at least to a considerable extent, occurs in the small intestine. Moreover, it is evident that fructose fermentation by the gut microbiota can produce metabolites such as acetate and ethanol, both of which cause potential deleterious health effects. Thus, in addition to the negative health effects of hepatic fructose catabolism, fructose fermentation by the gut microbiota can contribute to the production of (excessive) DNL substrates and the subsequent development of obesity,

hepatic steatosis and insulin resistance (Fig. 1) (Ameer et al., 2014).

**Fructose impairs intestinal barrier function mediated by the gut microbiota.** A number of studies have indicated that high fructose consumption impairs intestinal barrier function by reducing the expression of tight-junction proteins and decreasing mucus thickness, allowing for an increased translocation of bacterial endotoxins (Guo et al., 2021; Nier et al., 2019; Sellmann et al., 2015; Spruss et al., 2012; Volynets et al., 2017). These endotoxins can bind to toll-like receptor 4 in the liver, thereby activating nuclear factor-kB (NF-$\kappa$B) signalling pathways and resulting in the release of inflammatory cytokines such as TNF-$\alpha$ and IL-6. This, as a consequence, can promote insulin resistance and hepatic steatosis. Two studies demonstrated that impaired intestinal barrier function in mice is mediated by fructose-induced alterations in gut microbiota composition and microbial metabolites (Yu et al., 2023; Zhao et al., 2020b). These studies propose a protective role of *Akkermansia muciniphila* (Yu et al., 2023) and *Lactobacillus plantarum* (Zhao et al., 2020b), by attenuating fructose-induced inflammation and fructose-induced intestinal barrier impairment. However, in a recent randomized clinical trial involving obese humans, excessive fructose intake did not result in increased intestinal permeability or endotoxaemia (Alemán et al., 2021).

### Gut microbiota composition and ethnicity

*SIM* versus *colonic microbiota.* Due to the challenging and often invasive nature of small intestinal sampling, studies have frequently relied on ileostomy effluent samples, and only limited studies have examined the SIM composition in healthy individuals (Dlugosz et al., 2015; Gangping et al., 2015; Seekatz Anna et al., 2019; Shalon et al., 2023; Zilberstein et al., 2007). Analysis of these samples revealed that the SIM is subject to dynamic inter- and intraindividual variation and is less diverse when compared to the relatively stable and diverse colonic microbiota composition (Booijink et al., 2010). The dynamic nature of the SIM is likely due to dietary influences (Dagbasi et al. 2024; Zoetendal et al., 2012).

Although SIM composition varies along the different parts of the small intestine, the small intestine is generally characterized by a high relative abundance of the phyla Bacillota (formerly Firmicutes) and Pseudomonadota (formerly Proteobacteria) (Oren & Garrity, 2021), and a low relative abundance of Bacteroidota (formerly Bacteroidetes) (Yersin & Vonaesch 2024; Dlugosz et al., 2015; Gangping et al., 2015; Leite et al., 2020; Nagasue et al., 2022; Seekatz Anna et al., 2019; Shalon et al., 2023). This is in contrast to the high relative abundance of Bacillota and Bacteroidota among colon communities (Yersin & Vonaesch 2024; Gangping et al., 2015; Leite et al., 2020; Nagasue et al., 2022; Shalon et al., 2023). Bacillota species with a high relative abundance in the small intestine are primarily represented by LAB belonging to the families of the Lactobacillaceae, Streptococcaceae and Carnobacteriaceae, as well as the genus *Veillonella* (Dlugosz et al., 2015; Leite et al., 2020; Nagasue et al., 2022; Seekatz Anna et al., 2019; Yersin & Vonaesch 2024). Pseudomonadota within the small intestine are primarily represented by the bacterial families Neisseriaceae, Pasteurellaceae (including the abundant genera *Haemophilus* and *Actinobacillus*) and Enterobacteriaceae (including a high abundance of genus *Escherichia*) (Dlugosz et al., 2015; Leite et al., 2020).

*Ethnic variations in gut microbiota composition.* It has been reported that there is a difference in dietary added sugar intake between subjects of different ethnicities (Thompson et al., 2009), and it is likely that the (small) intestinal gut microbiota are involved in differential dietary sugar catabolism. Multiple studies have suggested that ethnicity plays a substantial role in the variations in gut microbiota composition among individuals, with those of the same ethnicity often exhibiting more similar gut microbiota profiles (Boulund et al., 2022; Deschasaux et al., 2018). Stearns et al. identified ethnic differences in the gut microbiota of infants in a Canadian cohort (Stearns et al., 2017). South Asian infants particularly exhibited a high relative abundance of the genera *Streptococcus, Enterococcus* and *Lactobacillus*, belonging to the order Lactobacillales, and of the phylum Bacillota. In contrast genera belonging to the order Clostridiales, including *Blautia, Pseudobutyrivibrio, Ruminococcus* and *Oscillospira*, were more prevalent among White Caucasian infants. These ethnic variations in the gut microbiota may be indicative of differences in the maternal and infant diets. It was demonstrated that significant ethnic differences in the gut microbiota emerge from the age of 3 months and persist throughout childhood (Mallott et al., 2023). *Haemophilus* spp. and *Prevotella copri* were more prevalent in Black children and adults than in White individuals (Mallott et al., 2023). Several studies have shown a positive correlation between the abundance of *P. copri* and obesity (Dong et al., 2022; Gong et al., 2024; Squillario et al., 2023; Stanislawski et al., 2019). One study, in particular, suggested that this correlation may be influenced by ethnicity, with a stronger association observed among Black and Hispanic populations (Stanislawski et al., 2019). On the contrary, *Faecalibacterium*, which has been associated with anti-inflammatory properties and the potential to promote gut health (Lopez-Siles et al., 2017; Sokol et al., 2008), was less abundant in Black children and adults than in White individuals (Mallott et al., 2023).

Individuals from a Dutch, multiethnic cohort, including participants of Dutch, Ghanaian, Moroccan, African Surinamese, South-Asian Surinamese and Turkish ethnicities, exhibited distinctive gut microbiota features, previously referred to as 'enterotypes' (Arumugam et al., 2011). The three enterotypes were distinguished by a high prevalence of *Bacteroides*, *Prevotella* or Clostridales (including *Coprococcus*, *Ruminococcus bromii* and *Oscillospira*). The Dutch exhibited a higher abundance of species within the Clostridiales group; the Surinamese demonstrated a high abundance of *Bacteroides*; and individuals of Moroccan, Turkish and Ghanaian descent exhibited elevated levels of *Prevotella* (Deschasaux et al., 2018). Of these enterotypes, a high abundance of *Prevotella* is typically associated with a diet rich in carbohydrates and simple sugars, whereas the *Bacteroides* enterotype has been associated with high protein and fat intake (Wu et al., 2011). Similarly, Dwiyanto et al. observed significant ethnic differences in gut microbiota composition in a multiethnic Malaysian cohort and suggested that dietary habits serve as a mediating factor for these ethnic differences within the same community (Dwiyanto et al., 2021). Brooks et al. studied ethnical gut microbiota differences among 1673 US individuals and found that 12 microbial taxa vary consistently in abundance across ethnic groups (Brooks et al., 2018). Most of these taxa have previously been shown to be heritable and linked to human genetic diversity.

These results show that ethnicity is a significant determinant of gut microbial differences, evident even in the early stages of life. However, it is important to note that these studies utilize faecal samples and therefore reflect only variations in the colonic microbiota. Diet is an important modulating factor of the gut microbiota and has been demonstrated to contribute to variations in gut microbiota composition between ethnic groups (Borrello et al., 2022). In this regard fructose, may contribute to differences in gut microbiota composition across ethnicities, given that its consumption varies among ethnic groups. Therefore, it is particularly relevant to explore the impact of fructose on the gut microbiota, to gain an in-depth understanding of its role in gut microbiota-related ethnic health disparities.

### Dietary fructose–gut microbiota–host effects

*Fructose alters gut microbiota composition and affects host health.* Diet is widely accepted as an imported modulating factor of the gut microbiota (David et al., 2014; Rinninella et al., 2023), particularly in the small intestine which is highly subject to dynamic (diet-induced) changes (Booijink et al., 2010; Zoetendal et al., 2012). The impact of high-fructose diets or fructose supplementation on gut microbiota composition and related metabolic effects is studied across various animal models (Table 1). These studies predominantly focus on the colonic microbiota, offering limited insights into the SIM.

Dietary fructose supplementation in rats for 15 weeks increased faecal Bacillota to Bacteroidota ratio (Akar et al., 2021). This was accompanied by elevated plasma levels of inflammatory cytokines, increased hepatic and ileal NF-$\kappa$B protein expression, suppression of ileal tight-junction proteins, enhanced hepatic lipogenic gene expression and reduced IRS-1 gene and protein expression in the liver. Treatment of these rats with kefir, which is predominantly composed of *Lactobacillus* (98.8%), reversed the fructose-induced Bacillota to Bacteroidota ratio and ameliorated the associated metabolic disturbances (Akar et al., 2021). This indicates that reshaping the microbiota through kefir supplementation exerts a protective effect against fructose-induced metabolic dysregulation.

This hypothesis is supported by evidence that supplementation of *L. plantarum* in high fructose-fed rats could reverse fructose-induced hepatic triglyceride accumulation together with attenuation of suppressed insulin signalling (Sumlu et al., 2022). Similarly, administration of *Lactobacillus reuteri* in rats fed a high-fructose diet ameliorated fructose-induced oxidative stress, insulin resistance, hepatic lipogenic gene expression and hepatic steatosis (Hsieh et al., 2013). These findings, consistent with those observed after kefir treatment, further underscore a potential protective role of certain *Lactobacillus* species in mitigating the adverse metabolic effects of a high-fructose diet. As previously described, *Lactobacillus* species have been identified as endogenous ethanol producers (Mbaye et al., 2024), including *L. reuteri* (Kandler et al., 1980; Oh et al., 2019). Therefore, it is important to note that bacteria within the genus *Lactobacillus*, or even specific *Lactobacillus* species, can exert both a protective role and harmful effects considering their role in endogenous ethanol production.

Only limited studies have examined the effects of fructose consumption on the gut microbiota in healthy humans. In healthy adolescents aged 12–19 years, there was a negative association between fructose consumption and the abundance of the genera *Streptococcus* and *Eubacterium* in the faecal microbiota (Jones et al., 2019). In healthy adult women, the effects of a high-fructose diet (100 g/day) through both a fruit-rich diet and supplementation of HFCS were observed (Beisner et al., 2020). After the fruit-rich diet an increased relative abundance of Bacillota, containing beneficial butyrate-forming genera including *Faecalibacterium, Anareostipes* and *Erysipelatoclostidium*, and decreased relative abundance of Bacteroidota was observed in stool samples. In contrast, compared to the fruit-rich diet, the HFCS-supplemented diet induced a decreased abundance of Bacillota and increased abundance of the phylum

**Table 1. Overview of fructose-induced alterations in gut microbiota composition reported in animal studies and its associated metabolic effects**

| Reference | Animal model | Fructose-related intervention | Gut microbiota alterations on taxonomic level | Assessed microbiota | Metabolic effects |
|---|---|---|---|---|---|
| (Jena et al., 2014) | Rats | 30 day high-fructose diet | Genus level:<br>↓ *Lactobacillus* | Faecal microbiota | Increased fasting blood glucose, oral glucose tolerance test values, plasma lipids/AST/ALT and histological liver steatosis. |
| (Di Luccia et al., 2015) | Rats | 8 week high-fructose diet | Family level:<br>↑Coriobacteriaceae<br>Genus level:<br>↑ *Coprococcus, Ruminococcus, Coprobacillus, Roseburia*<br>↓ *Bacteroides, Lactobacillus, Clostridium*<br>Antibiotic treatment and a faecal transplant from rats fed with a standard diet restored the representativeness of *Coprococcus* and *Ruminococcus* | Caecal microbiota | Elevated markers of metabolic syndrome, inflammation and oxidative stress. Antibiotic treatment reversed these effects, and a faecal transplant from rats fed with a standard diet partially reversed them. |
| (Crescenzo et al., 2017) | Rats | 8 week high-fructose diet | Family level:<br>↓Clostridiaceae<br>Genus level:<br>↑ *Coprococcus, Ruminococcus, Clostridium*<br>These alterations were eliminated by antibiotic treatment | Caecal microbiota | Fasting hyperinsulinaemia and increased hepatic insulin resistance index. Increased portal levels of TNF-$\alpha$, lipopolysaccharide and non-esterified fatty acids. Decrease in ileal tight-junction protein occludin expression. Increased ileal inflammation. These effects were reversed by antibiotic treatment. |
| (Volynets et al., 2017) | Rats | 12 week fructose supplementation to a control diet or Western-style diet | ↑ Bacillota:Bacteroidota<br>Phylum level:<br>↓ Bacteroidota<br>Genus level:<br>↑ *Parabacteroides, Bifidobacterium, Alistipes, Tyzzerella, Allobaculum, Acetatifactor, Akkermansia*<br>↓ *Barnesiella, Lactobacillus, Intestinimonas, Candidatus, Arthromitus, Ruminiclostridium* | Faecal microbiota | Increased endotoxin levels within the portal vein, intestinal barrier impairment and increased liver to body weight ratio, likely reflecting subsequent liver steatosis. |

(*Continued*)

**Table 1. (Continued)**

| Reference | Animal model | Fructose-related intervention | Gut microbiota alterations on taxonomic level | Assessed microbiota | Metabolic effects |
|---|---|---|---|---|---|
| (Do et al., 2018) | Mice | 12 week high-fructose diet | Phylum level:<br>↑ Pseudomonadota<br>↓ Bacteroidota<br>Genus level:<br>↑ *Desulfovibrio vulgaris*<br>↓ *Muribaculum intestinale* | Faecal microbiota | Increased serum levels of glucose/LDL and total cholesterol/endotoxins, increased inflammatory cytokines in the colon and liver, increased hepatic steatosis, reduced expression of tight-junction proteins and increased gut permeability. |
| (Mastrocola et al., 2018) | Mice | 12 week 60% fructose solid diet (S-Fr) or standard diet + 60% fructose syrup (L-Fr) | ↓ Bacillota:Bacteroidota<br>Genus level:<br>↑*L-Ruminococcus*, *R-Ruminococcus, Coprococcus*<br>Alterations in mice fed with fructose compared to standard diet | Ileal microbiota | Increased accumulation of advanced glycation end products, decreased ileal expression of tight-junction proteins, increased protein levels of TLR-4 and NLRP3 in liver, increased hepatic steatosis and increased markers of fibrosis. |
| (Silva et al., 2018) | Mice | 10 week high-fructose (60%) diet | Genus level:<br>↑*Lactobacillus* | Faecal microbiota | Intestinal metabolite changes:<br>decreased butyrate and glutamate and increased fructose, succinate, taurine, tyrosine and xylose. |
| (Li et al., 2019) | Mice | 8 week high-fructose diet | Phylum level:<br>↑ Pseudomonadota<br>↓ Bacteroidota<br>Family level:<br>↑ Ruminococcaceae<br>Genus level:<br>↑ *Mucispirillum, Helicobacter* | Faecal microbiota | Intestinal barrier impairment. |
| (Curtasu et al., 2020) | Pigs | 20 week 20% fructose supplementation to a high-fat diet | Family level:<br>↑ Lachnospiraceae, Clostridiaceae, Erysipelotrichaceae, Peptostreptococcaceae, Mogibacteriaceae, Coriobacteriaceae<br>Genus level:<br>↑*Roseburia, Coprococcus*, *Dorea*, *Blautia*, *Ruminococcus* | Faecal microbiota | — |

(*Continued*)

**Table 1. (Continued)**

| Reference | Animal model | Fructose-related intervention | Gut microbiota alterations on taxonomic level | Assessed microbiota | Metabolic effects |
|---|---|---|---|---|---|
| (Wang et al., 2020) | Rats | 20 week high-fructose diet (10.5 g/kg/day) | Genus level:<br>↑ *Lachnospira, Marvinbryantia, Parasutterella*, *Blantia* | Colonic microbiota | Decreased expression of colonic tight-junction proteins, increased inflammatory cell infiltration in the pancreas and colon and increased hepatic steatosis. |
| (Akar et al., 2021) | Rats | 15 week fructose supplementation with a 20% solution | ↑ Bacillota:Bacteroidota<br>Phylum level:<br>↑ Bacillota<br>↓ Bacteroidota, Actinomycetota | Faecal microbiota | Elevated plasma inflammatory cytokines, increased hepatic and ileal NF-$\kappa$B protein expression, decreased ileal tight-junction proteins levels, enhanced hepatic lipogenic gene expression and reduced IRS-1 gene and protein expression in the liver. |
| (Bhat et al., 2021) | Mice | 3 week HFCS supplementation | Family level:<br>↑ Erysipelotrichaceae<br>↓ Ruminococcaceae<br>Genus level:<br>↑ *Bifidobacterium* | Faecal microbiota | Significantly increased mRNA levels of key lipogenic enzymes (e.g. ACC, FAS, ChREBP and SREBP-1c). Impaired glucose tolerance and increased serum levels of insulin and adiponectin in males. Increased fat mass and leptin plasma levels in females. |
| (Guo et al., 2021) | Piglets | 35 day fructose supplementation | Phylum level:<br>↑ Bacteroidota, Actinomycetota, Mycoplasmatota<br>↓ Bacillota, Pseudomonadota<br>Genus level:<br>↑ *Streptococcus, Faecalibacterium*<br>↓*Bacillus, Paecalibacterium, Enterococcus, Cronobacter, Alkaliphilus* | Ileal microbiota | Decreased ileal tight-junction gene expressions. |

(*Continued*)

**Table 1. (Continued)**

| Reference | Animal model | Fructose-related intervention | Gut microbiota alterations on taxonomic level | Assessed microbiota | Metabolic effects |
|---|---|---|---|---|---|
| (Montrose et al., 2021) | Mice | 1- or 2 week high-fructose diet | Species level:<br>↑*Akkermansia muciniphila, Clostridium* sp., *Roseburia* sp., *Lachnoclostridium clostridium aldenense, Lachnoclostridium clostridiu scindens*<br>Species level:<br>↓ *Clostridium disporicum, Lactobacillus johnsonii, Bacteroides acidifaciens, Allobaculum* sp. | Faecal microbiota | Worsening of colitis. |
| (Szabó et al., 2021) | Rats | 30 day high-fructose (65%) diet | Phylum level:<br>↓ Bacillota, Bacteroidota<br>↑Pseudomonadota, Actinomycetota, Verrucomicrobiota | Caecal microbiota | Increased lipid content of the liver, mild increased insulin resistance. |
| (Tan et al., 2021) | Mice | 8 week high-fructose diet | ↑ Bacillota:Bacteroidota<br>Phylum level:<br>↑ Actinomycetota, Deferribacterota, Verrucomicrobiiota<br>Genus level:<br>↑ *Bifidobacterium, Enterococcus, Bacteroides*, *Akkermansia*, *Lactobacillus, Ruminiclostridium, Romboutsia, Turicibacter* | Faecal microbiota | Increased serum levels of pro-inflammatory cytokines and inflammatory cell infiltration in the intestine. |
| (Zhou et al., 2023) | Mice | 12 week high-fructose (60%) diet | ↑ Bacillota:Bacteroidota<br>Phylum level:<br>↑ Bacillota<br>↓ Bacteroidota<br>Genus level:<br>↑*Rikenellaceae*, *Lachnoclostridium*, *Colidextribacter*, *Blautia*, *Alistipes*, *Bacteroides* and *Oscillibacter*a | Faecal microbiota | Decreased expression of colonic tight-junction proteins. Increased inflammatory cell infiltration in the colon. Increased plasma levels of TNF-$\alpha$, IL-1$\beta$ and IL-6. Increased T-helper type 1 cells and decreased regulatory T cells in the mesenteric lymph nodes. Increased mRNA expression levels of lipogenic enzymes (*FAS*, *ACC1*, *CD36*, *ChREBP* and *SREBP-1c*). Increased insulin resistance (IR) and hepatic steatosis. Faecal microbiota transplantation alleviated the fructose-induced IR and hepatic steatosis |

Abbreviations: ACC1, acetyl-CoA carboxylase 1; ALT, alanine transaminase; AST, aspartate transaminase; ChREBP, carbohydrate response element binding protein; FAS, fatty-acid synthase; HFCS, high-fructose corn syrup; IRS-1, insulin receptor substrate 1; LDL, low-density lipoprotein; SREBP-1c, sterol regulatory element binding protein 1c; TLR-4, toll-like receptor 4.

Bacteroidota and genus *Ruminococcus*. This suggests that the different formulations of fructose ingestion have diverse effects on the gut microbiota, with HFCS supplementation exhibiting more unfavourable effects.

The results of these studies demonstrate that diet-derived fructose can alter the constituent gut microbiota, with a broad range of alterations being reported. One of the most commonly observed fructose-induced changes in the gut microbiota includes an increase in the abundance of Bacillota and a decrease in the abundance of Bacteroidota, resulting in a higher Bacillota to Bacteroidota ratio. An increased Bacillota to Bacteroidota ratio is often regarded as dysbiosis and has been associated with obesity, although this association remains controversial (Magne et al., 2020). Together with the observed fructose-induced changes in gut microbiota composition, negative metabolic effects promoting increased pro-inflammatory cytokines levels, intestinal barrier impairment, insulin resistance and hepatic steatosis have been repeatedly described in animal models. Moreover, a potential protective role has been described for *Lactobacillus* species, in ameliorating these deleterious fructose-induced metabolic effects. However, further research is needed to confirm their applicability in humans.

## Conclusion

This review has highlighted the negative metabolic effects of fructose catabolism and the key role of the gut microbiota. Notably, there are significant differences in gut microbiota composition across ethnic groups, with diet being a major influencing factor. Additionally, fructose intake varies between ethnic groups due to differences in dietary habits, although data on this topic is still limited. These variations in fructose consumption may further shape gut microbiota composition and SIM metabolism among different ethnicities. Therefore, both ethnicity and variations in fructose intake could potentially contribute to health disparities. Thus, a comprehensive understanding of these interactions is crucial for the advancement of personalized nutrition strategies, with the ultimate objective of addressing potential health disparities related to fructose catabolism.

We are currently conducting an ongoing double-blind randomized controlled trial with the aim of gaining further insight into the effect of high-dietary fructose consumption on the acute fructose kinetics and its metabolic effects in T2D individuals from White and South-Asian Surinamese descent (the 'ERIE' trial, registered at clinicaltrials.gov as NCT05717608). Moreover, this trial will assess both host and gut microbial fructose catabolism and its correlation with oral and faecal gut microbial composition as well as clinical important health parameters.

Nevertheless, it is important to note that current research on gut microbiota in relation to ethnicity and fructose–gut microbiota interactions predominantly pertains to the faecal microbiota. Still very little is known about the effects on the SIM, which is of great interest considering its role in fructose catabolism. Future research in this area should therefore also focus on the role of the small intestine microbiota. Novel techniques to sample SIM, including capsule-based sampling methods (Rezaei Nejad et al., 2019; Shalon et al., 2023; Tang et al., 2020; Waimin et al., 2020), could advance research in this field.

## References

Aeberli, I., Hochuli, M., Gerber, P. A., Sze, L., Murer, S. B., Tappy, L., Spinas, G. A. & Berneis, K. (2012). Moderate amounts of fructose consumption impair insulin sensitivity in healthy young men: A randomized controlled trial. *Diabetes Care*, **36**(1), 150–156.

Aguirre, V., Werner, E. D., Giraud, J., Lee, Y. H., Shoelson, S. E. & White, M. F. (2002). Phosphorylation of $Ser^{307}$ in insulin receptor substrate-1 blocks interactions with the insulin receptor and inhibits insulin action *. *Journal of Biological Chemistry*, **277**(2), 1531–1537.

Agyemang, C., van der Linden, E. L. & Bennet, L. (2021). Type 2 diabetes burden among migrants in Europe: Unravelling the causal pathways. *Diabetologia*, **64**(12), 2665–2675.

Akar, F., Sumlu, E., Alçığır, M. E., Bostancı, A. & Sadi, G. (2021). Potential mechanistic pathways underlying intestinal and hepatic effects of kefir in high-fructose-fed rats. *Food Research International*, **143**, 110287.

Alemán, J. O., Henderson, W. A., Walker, J. M., Ronning, A., Jones, D. R., Walter, P. J., Daniel, S. G., Bittinger, K., Vaughan, R., MacArthur, R., Chen, K., Breslow, J. L. & Holt, P. R. (2021). Excess dietary fructose does not alter gut microbiota or permeability in humans: A pilot randomized controlled study. *Journal of Clinical and Translational Science*, **5**(1), e143.

Ameer, F., Scandiuzzi, L., Hasnain, S., Kalbacher, H. & Zaidi, N. (2014). De novo lipogenesis in health and disease. *Metabolism*, **63**(7), 895–902.

Arumugam, M., Raes, J., Pelletier, E., Le Paslier, D., Yamada, T., Mende, D. R., Fernandes, G. R., Tap, J., Bruls, T., Batto, J.-M., Bertalan, M., Borruel, N., Casellas, F., Fernandez, L., Gautier, L., Hansen, T., Hattori, M., Hayashi, T., Kleerebezem, M., … Bork, P. (2011). Enterotypes of the human gut microbiome. *Nature*, **473**(7346), 174–180.

Balvers, M., de Goffau, M., van Riel, N., van den Born, B.-J., Galenkamp, H., Zwinderman, K., Nieuwdorp, M. & Levin, E (2024). Ethnic variations in metabolic syndrome components and their associations with the gut microbiota: The HELIUS study. *Genome Medicine*, **16**(1), 41.

Beisner, J., Gonzalez-Granda, A., Basrai, M., Damms-Machado, A. & Bischoff, S. C. (2020). Fructose-induced intestinal microbiota shift following two types of short-term high-fructose dietary phases. In *Nutrients*.

Berg, G., Rybakova, D., Fischer, D., Cernava, T., Vergès, M.-C. C., Charles, T., Chen, X., Cocolin, L., Eversole, K., Corral, G. H., Kazou, M., Kinkel, L., Lange, L., Lima, N., Loy, A., Macklin, J. A., Maguin, E., Mauchline, T., Mcclure, R., … Schloter, M. (2020). Microbiome definition re-visited: Old concepts and new challenges. *Microbiome*, **8**(1), 103.

Beyer, P. L., Caviar, E. M. & McCallum, R. W. (2005). Fructose intake at current levels in the United States may cause gastrointestinal distress in normal adults. *Journal of the American Dietetic Association*, **105**(10), 1559–1566.

Bhat, S. F., Pinney, S. E., Kennedy, K. M., McCourt, C. R., Mundy, M. A., Surette, M. G., Sloboda, D. M. & Simmons, R. A. (2021). Exposure to high fructose corn syrup during adolescence in the mouse alters hepatic metabolism and the microbiome in a sex-specific manner. *The Journal of Physiology*, **599**(5), 1487–1511.

Bode, J. C., Zelder, O., Rumpelt, H. J. & Wittkampy, U. (1973). Depletion of liver adenosine phosphates and metabolic effects of intravenous infusion of fructose or sorbitol in man and in the rat. *European Journal of Clinical Investigation*, **3**(5), 436–441.

Boden, G., She, P., Mozzoli, M., Cheung, P., Gumireddy, K., Reddy, P., Xiang, X., Luo, Z. & Ruderman, N. (2005). Free fatty acids produce insulin resistance and activate the proinflammatory nuclear Factor-$\kappa$B pathway in rat liver. *Diabetes*, **54**(12), 3458–3465.

Boehm, R., Cooksey Stowers, K., Schneider, G. E. & Schwartz, M. B. (2022). Race, ethnicity, and neighborhood food environment are associated with adolescent sugary drink consumption during a 5-year community campaign. *Journal of Racial and Ethnic Health Disparities*, **9**(4), 1335–1346.

Booijink, C. G. M., El-Aidy, S., Rajilić-Stojanović, M., Heilig, H. G. H. J., Troost, F. J., Smidt, H., Kleerebezem, M., De Vos, W. M., Zoetendal, E. G. (2010). High temporal and inter-individual variation detected in the human ileal microbiota. *Environmental Microbiology*, **12**(12), 3213–3227.

Borrello, K., Lim, U., Park, S.-Y., Monroe, K. R., Maskarinec, G., Boushey, C. J., Wilkens, L. R., Randolph, T. W., Le Marchand, L., Hullar, M. A. & Lampe, J. W (2022). Dietary intake mediates ethnic differences in gut microbial composition. In *Nutrients*.

Boulund, U., Bastos, D. M., Ferwerda, B., van den Born, B.-J., Pinto-Sietsma, S.-J., Galenkamp, H., Levin, E., Groen, A. K., Zwinderman, A. H. & Nieuwdorp, M. (2022). Gut microbiome associations with host genotype vary across ethnicities and potentially influence cardiometabolic traits. *Cell Host & Microbe*, **30**(10), 1464–1480.e1466.

Braga, T. T., Forni, M. F., Correa-Costa, M., Ramos, R. N., Barbuto, J. A., Branco, P., Castoldi, A., Hiyane, M. I., Davanso, M. R., Latz, E., Franklin, B. S., Kowaltowski, A. J. & Camara, N. O. S. (2017). Soluble uric acid activates the NLRP3 inflammasome. *Scientific Reports*, **7**(1), 39884.

Bray, G. A., Nielsen, S. J. & Popkin, B. M. (2004). Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *The American Journal of Clinical Nutrition*, **79**(4), 537–543.

Brooks, A. W., Priya, S., Blekhman, R. & Bordenstein, S. R. (2018). Gut microbiota diversity across ethnicities in the United States. *PLoS Biology*, **16**(12), e2006842.

Burant, C. F. & Saxena, M. (1994). Rapid reversible substrate regulation of fructose transporter expression in rat small intestine and kidney. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, **267**(1), G71–G79.

Burant, C. F., Takeda, J., Brot-Laroche, E., Bell, G.I. & Davidson, N. O. (1992). Fructose transporter in human spermatozoa and small intestine is GLUT5. *Journal of Biological Chemistry*, **267**(21), 14523–14526.

Carpentier, A. C. (2021). 100th anniversary of the discovery of insulin perspective: Insulin and adipose tissue fatty acid metabolism. *American Journal of Physiology-Endocrinology and Metabolism*, **320**(4), E653–E670.

Cheeseman, C. I. (1993). GLUT2 is the transporter for fructose across the rat intestinal basolateral membrane. *Gastroenterology*, **105**(4), 1050–1056.

Chen, L., Chen, R., Wang, H. & Liang, F. (2015). Mechanisms linking inflammation to insulin resistance. *International Journal of Endocrinology*, **2015**, 508409.

Choi, S. M., Tucker, D. F., Gross, D. N., Easton, R. M., DiPilato, L. M., Dean, A. S., Monks, B. R. & Birnbaum, M. J. (2010). Insulin regulates adipocyte lipolysis via an Akt-independent signaling pathway. *Molecular and Cellular Biology*, **30**(21), 5009–5020.

Ciani, M., Comitini, F. & Mannazzu, I. (2008). Fermentation. In *Encyclopedia of Ecology*, ed. S. E. Jørgensen & B. D. Fath, pp. 1548–1557. Academic Press.

Crescenzo, R., Mazzoli, A., Di Luccia, B., Bianco, F., Cancelliere, R., Cigliano, L., Liverini, G., Baccigalupi, L. & Iossa, S. (2017). Dietary fructose causes defective insulin signalling and ceramide accumulation in the liver that can be reversed by gut microbiota modulation. *Food & Nutrition Research*, **61**(1), 1331657.

Curtasu, M. V., Tafintseva, V., Bendiks, Z. A., Marco, M. L., Kohler, A., Xu, Y., Nørskov, N. P., Nygaard Lærke, H., Bach Knudsen, K. E. & Hedemann, M. S. (2020). Obesity-related metabolome and gut microbiota profiles of juvenile Göttingen Minipigs—long-term intake of fructose and resistant starch. In *Metabolites*.

Dagbasi, A., Byrne, C., Blunt, D., Serrano-Contreras, J. I., Becker, G. F., Blanco, J. M., Camuzeaux, S., Chambers, E., Danckert, N., Edwards, C., Bernal, A., Garcia, M. V., Hanyaloglu, A., Holmes, E., Ma, Y., Marchesi, J., Martinez-Gili, L., Mendoza, L., Tashkova, M., … Frost, G. (2024). Diet shapes the metabolite profile in the intact human ileum, which affects PYY release. *Science Translational Medicine*, **16**(752), eadm8132.

Dai, J., Soto, M. J., Dunn, C. G. & Bleich, S. N (2021). Trends and patterns in sugar-sweetened beverage consumption among children and adults by race and/or ethnicity, 2003–2018. *Public Health Nutrition*, **24**(9), 2405–2410.

David, E. S., Cingari, D. S. & Ferraris, R. P. (1995). Dietary induction of intestinal fructose absorption in weaning rats. *Pediatric Research*, **37**(6), 777–782.

David, L. A., Maurice, C. F., Carmody, R. N., Gootenberg, D. B., Button, J. E., Wolfe, B. E., Ling, A. V., Devlin, A. S., Varma, Y., Fischbach, M. A., Biddinger, S. B., Dutton, R. J. & Turnbaugh, P. J. (2014). Diet rapidly and reproducibly alters the human gut microbiome. *Nature*, **505**(7484), 559–563.

de Wilde, J. A., Meeuwsen, R. C. & Middelkoop, B. J. (2018). Growing ethnic disparities in prevalence of overweight and obesity in children 2–15 years in the Netherlands. *European Journal of Public Health*, **28**(6), 1023–1028.

denBesten, G., Bleeker, A., Gerding, A., van Eunen, K., Havinga, R., van Dijk, T. H., Oosterveer, M. H., Jonker, J. W., Groen, A. K., Reijngoud, D.-J. & Bakker, B. M. (2015). Short-chain fatty acids protect against high-fat diet–induced obesity via a PPAR$\gamma$-dependent switch from lipogenesis to fat oxidation. *Diabetes*, **64**(7), 2398–2408.

Deschasaux, M., Bouter, K. E., Prodan, A., Levin, E., Groen, A. K., Herrema, H., Tremaroli, V., Bakker, G. J., Attaye, I., Pinto-Sietsma, S.-J., van Raalte, D. H., Snijder, M. B., Nicolaou, M., Peters, R., Zwinderman, A. H., Bäckhed, F. & Nieuwdorp, M. (2018). Depicting the composition of gut microbiota in a population with varied ethnic origins but shared geography. *Nature Medicine*, **24**(10), 1526–1531.

Di Luccia, B., Crescenzo, R., Mazzoli, A., Cigliano, L., Venditti, P., Walser, J.-C., Widmer, A., Baccigalupi, L., Ricca, E. & Iossa, S. (2015). Rescue of fructose-induced metabolic syndrome by antibiotics or faecal transplantation in a rat model of obesity. *PLoS ONE*, **10**(8), e0134893.

DiFrancesco, L., Fulgoni V. L., 3rd, Gaine, P. C., Scott, M. O. & Ricciuto, L. (2022). Trends in added sugars intake and sources among U.S. adults using the National Health and Nutrition Examination Survey (NHANES) 2001–2018. *Frontiers in Nutrition*, **9**, 897952.

Dlugosz, A., Winckler, B., Lundin, E., Zakikhany, K., Sandström, G., Ye, W., Engstrand, L. & Lindberg, G. (2015). No difference in small bowel microbiota between patients with irritable bowel syndrome and healthy controls. *Scientific Reports*, **5**(1), 8508.

Do, M. H., Lee, E., Oh, M.-J., Kim, Y. & Park, H-Y. (2018). High-glucose or-fructose diet cause changes of the gut microbiota and metabolic disorders in mice without body weight change. In *Nutrients*.

Dong, T. S., Guan, M., Mayer, E. A., Stains, J., Liu, C., Vora, P., Jacobs, J. P., Lagishetty, V., Chang, L., Barry, R. L. & Gupta, A. (2022). Obesity is associated with a distinct brain-gut microbiome signature that connects Prevotella and Bacteroides to the brain's reward center. *Gut Microbes*, **14**(1), 2051999.

Dwiyanto, J., Hussain, M. H., Reidpath, D., Ong, K. S., Qasim, A., Lee, S. W. H., Lee, S. M., Foo, S. C., Chong, C. W. & Rahman, S. (2021). Ethnicity influences the gut microbiota of individuals sharing a geographical location: a cross-sectional study from a middle-income country. *Scientific Reports*, **11**(1), 2618.

Dyer, J., Wood, I. S., Palejwala, A., Ellis, A. & Shirazi-Beechey, S. P. (2002). Expression of monosaccharide transporters in intestine of diabetic humans. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, **282**(2), G241–G248.

Elshaghabee, F. M. F., Bockelmann, W., Meske, D., de Vrese, M., Walte, H.-G., Schrezenmeir, J. & Heller, K. J. (2016). Ethanol production by selected intestinal microorganisms and lactic acid bacteria growing under different nutritional conditions. *Frontiers in Microbiology*, **7**, 00047.

Federico, A., Rosato, V., Masarone, M., Torre, P., Dallio, M., Romeo, M. & Persico, M. (2021). The role of fructose in non-alcoholic steatohepatitis: Old relationship and new insights. *Nutrients*, **13**(4), 1314.

Gangping, L., Min, Y., Kan, Z., Lei, Z., Lugao, T., Shangze, L., Yu, J., Wei, Q., Hanhua, X., Rong, L. & Yu, F. (2015). Diversity of duodenal and rectal microbiota in biopsy tissues and luminal contents in healthy volunteers. *Journal of Microbiology and Biotechnology*, **25**(7), 1136–1145.

Gao, Z., Hwang, D., Bataille, F., Lefevre, M., York, D., Quon, M. J. & Ye, J. (2002). Serine phosphorylation of insulin receptor substrate 1 by inhibitor $\kappa$B kinase complex*. *Journal of Biological Chemistry*, **277**(50), 48115–48121.

Gibson, P. R., Newnham, E., Barrett, J. S., Shepherd, S. J. & Muir, J. G. (2007). Review article: Fructose malabsorption and the bigger picture. *Alimentary Pharmacology & Therapeutics*, **25**(4), 349–363.

Gong, J., Zhang, Q., Hu, R., Yang, X., Fang, C., Yao, L., Lv, J., Wang, L., Shi, M., Zhang, W., Ma, S., Xiang, H., Zhang, H., Hou, D.-X., Yin, Y., He, J., Peng, L. & Wu, S. (2024). Effects of Prevotella copri on insulin, gut microbiota and bile acids. *Gut Microbes*, **16**(1), 2340487.

Guo, P., Wang, H., Ji, L., Song, P. &. Ma, X. (2021). Impacts of fructose on intestinal barrier function, inflammation and microbiota in a piglet model. In *Nutrients*.

Hales, C. M. C. M., Fryar, C. D., Ogden, C. L. (2020). *Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017–2018*. Hyattsville, MD: National Center for Health Statistics. NCHS Data Brief, no 360.

Hediger, M. A. & Rhoads, D. B. (1994). Molecular physiology of sodium-glucose cotransporters. *Physiological Reviews*, **74**(4), 993–1026.

Heinz, F., Lamprecht, W. & Kirsch, J. (1968). Enzymes of fructose metabolism in human liver. *Journal of Clinical Investigation*, **47**(8), 1826–1832.

Hirosumi, J., Tuncman, G., Chang, L., Görgün, C. Z., Uysal, K. T., Maeda, K., Karin, M. & Hotamisligil, G. S. (2002). A central role for JNK in obesity and insulin resistance. *Nature*, **420**(6913), 333–336.

Hsieh, F.-C., Lee, C.-L., Chai, C.-Y., Chen, W.-T., Lu, Y.-C. &. Wu, C.-S. (2013). Oral administration of Lactobacillus reuteri GMNL-263 improves insulin resistance and ameliorates hepatic steatosis in high fructose-fed rats. *Nutrition & Metabolism*, **10**(1), 35.

Jang, C., Hui, S., Lu, W., Cowan, A. J., Morscher, R. J., Lee, G., Liu, W., Tesz, G. J., Birnbaum, M. J. & Rabinowitz, J. D. (2018). The small intestine converts dietary fructose into glucose and organic acids. *Cell Metabolism*, **27**(2), 351–361.e353.

Jang, C., Wada, S., Yang, S., Gosis, B., Zeng, X., Zhang, Z., Shen, Y., Lee, G., Arany, Z. & Rabinowitz, J. D. (2020). The small intestine shields the liver from fructose-induced steatosis. *Nature Metabolism*, **2**(7), 586–593.

Jegatheesan, P. & De Bandt, J. P. (2017). Fructose and NAFLD: The multifaceted aspects of fructose metabolism. *Nutrients*, **9**(3), 230.

Jena, P. K., Singh, S., Prajapati, B., Nareshkumar, G., Mehta, T. & Seshadri, S. (2014). Impact of targeted specific antibiotic delivery for gut microbiota modulation on high-fructose-fed rats. *Applied Biochemistry and Biotechnology*, **172**(8), 3810–3826.

Johnson, R. J., Segal, M. S., Sautin, Y., Nakagawa, T., Feig, D. I., Kang, D.-H., Gersch, M. S., Benner, S. & Sánchez-Lozada, L. G. (2007). Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease. *The American Journal of Clinical Nutrition*, **86**(4), 899–906.

Jones, R. B., Alderete, T. L., Kim, J. S., Millstein, J., Gilliland, F. D. & Goran, M. I. (2019). High intake of dietary fructose in overweight/obese teenagers associated with depletion of Eubacterium and Streptococcus in gut microbiome. *Gut Microbes*, **10**(6), 712–719.

Jung, S., Bae, H., Song, W. S. & Jang, C. (2022). Dietary fructose and fructose-induced pathologies. *Annual Review of Nutrition*, **42**(1), 45–66.

Kandler, O., Stetter, K.-O. &. Köhl, R. (1980). Lactobacillus reuteri sp. nov., a New Species of Heterofermentative Lactobacilli. *Zentralblatt für Bakteriologie: I Abt Originale C: Allgemeine, angewandte und ökologische Mikrobiologie*, **1**(3), 264–269.

Kane, S., Seatter, M. J. & Gould, G. W. (1997). Functional studies of human GLUT5: Effect of pH on substrate selection and an analysis of substrate interactions. *Biochemical and Biophysical Research Communications*, **238**(2), 503–505.

Kastl A. J., Jr., Terry, N. A., Wu, G. D. & Albenberg, L. G. (2020). The structure and function of the human small intestinal microbiota: Current understanding and future directions. *Cellular and Molecular Gastroenterology and Hepatology*, **9**(1), 33–45.

Kellett, G. L. (2001). The facilitated component of intestinal glucose absorption. *The Journal of Physiology*, **531**(3), 585–595.

Kellett, G. L. & Brot-Laroche, E. (2005). Apical GLUT2 : A major pathway of intestinal sugar absorption. *Diabetes*, **54**(10), 3056–3062.

Koo, H.-Y., Miyashita, M., Simon Cho, B. H. & Nakamura, M. T. (2009). Replacing dietary glucose with fructose increases ChREBP activity and SREBP-1 protein in rat liver nucleus. *Biochemical and Biophysical Research Communications*, **390**(2), 285–289.

Lanaspa, M. A., Sanchez-Lozada, L. G., Choi, Y.-J., Cicerchi, C., Kanbay, M., Roncal-Jimenez, C. A., Ishimoto, T., Li, N., Marek, G., Duranay, M., Schreiner, G., Rodriguez-Iturbe, B., Nakagawa, T., Kang, D.-H., Sautin, Y. Y. & Johnson, R. J. (2012). Uric Acid Induces Hepatic Steatosis by Generation of Mitochondrial Oxidative Stress: POTENTIAL ROLE IN FRUCTOSE-DEPENDENT AND -INDEPENDENT FATTY LIVER*. *Journal of Biological Chemistry*, **287**(48), 40732–40744.

Leite, G. G. S., Weitsman, S., Parodi, G., Celly, S., Sedighi, R., Sanchez, M., Morales, W., Villanueva-Millan, M. J., Barlow, G. M., Mathur, R., Lo, S. K., Jamil, L. H., Paski, S., Rezaie, A. & Pimentel, M. (2020). Mapping the segmental microbiomes in the human small bowel in comparison with stool: A REIMAGINE Study. *Digestive Diseases and Sciences*, **65**(9), 2595–2604.

Li, J.-M., Yu, R., Zhang, L.-P., Wen, S.-Y., Wang, S.-J., Zhang, X.-Y., Xu, Q. & Kong, L-D. (2019). Dietary fructose-induced gut dysbiosis promotes mouse hippocampal neuroinflammation: a benefit of short-chain fatty acids. *Microbiome*, **7**(1), 98.

Lim, J., Lee, H., Hojung, M., Song, J. (2009). Coupling mitochondrial dysfunction to endoplasmic reticulum stress response: A molecular mechanism leading to hepatic insulin resistance. *Cellular Signalling*, **21**(1), 169–177.

Lim, J. S., Mietus-Snyder, M., Valente, A., Schwarz, J.-M. &. Lustig, R. H. (2010). The role of fructose in the pathogenesis of NAFLD and the metabolic syndrome. *Nature Reviews Gastroenterology & Hepatology*, **7**, 251–264.

Liu, J. & Mozaffarian, D. (2024). Trends in diet quality among U.S. adults from 1999 to 2020 by race, ethnicity, and socioeconomic disadvantage. *Annals of Internal Medicine*, **177**(7), 841–850.

Lopez-Siles, M., Duncan, S. H., Garcia-Gil, L. J. & Martinez-Medina, M. (2017). Faecalibacterium prausnitzii: from microbiology to diagnostics and prognostics. *The International Society for Microbial Ecology Journal*, **11**(4), 841–852.

Lustig, R. (2013). Fructose: It's "Alcohol Without the Buzz". *Advances in nutrition (Bethesda, Md)*, **4**(2), 226–235.

Magne, F., Gotteland, M., Gauthier, L., Zazueta, A., Pesoa, S., Navarrete, P. & Balamurugan, R. (2020). The firmicutes/bacteroidetes ratio: A relevant marker of gut dysbiosis in obese patients? *Nutrients*, **12**(5), 1474.

Mallott, E. K., Sitarik, A. R., Leve, L. D., Cioffi, C., Camargo, C. A., Jr., Hasegawa, K. & Bordenstein, S. R. (2023). Human microbiome variation associated with race and ethnicity emerges as early as 3 months of age. *PLoS Biology*, **21**(8), e3002230.

Marchesini, G., Brizi, M., Bianchi, G., Tomassetti, S., Bugianesi, E., Lenzi, M., McCullough, A. J., Natale, S., Forlani, G. & Melchionda, N. (2001). Nonalcoholic fatty liver disease: A feature of the metabolic syndrome. *Diabetes*, **50**(8), 1844–1850.

Mastrocola, R., Ferrocino, I., Liberto, E., Chiazza, F., Cento, A. S., Collotta, D., Querio, G., Nigro, D., Bitonto, V., Cutrin, J. C., Rantsiou, K., Durante, M., Masini, E., Aragno, M., Cordero, C., Cocolin, L. & Collino, M. (2018). Fructose liquid and solid formulations differently affect gut integrity, microbiota composition and related liver toxicity: A comparative in vivo study. *The Journal of Nutritional Biochemistry*, **55**, 185–199.

Mbaye, B., Wasfy, R. M., Alou, M. T., Borentain, P., Gerolami, R., Dufour, J.-C. &. Million, M. (2024). A catalog of ethanol-producing microbes in humans. *Future Microbiology*, **19**(8), 697–714.

Meeks, K. A. C., Freitas-Da-Silva, D., Adeyemo, A., Beune, E., Modesti, P. A., Stronks, K., Zafarmand, M. H. & Agyemang, C. (2016). Disparities in type 2 diabetes prevalence among ethnic minority groups resident in Europe: A systematic review and meta-analysis. *Internal and Emergency Medicine*, **11**(3), 327–340.

Meijnikman, A. S., Davids, M., Herrema, H., Aydin, O., Tremaroli, V., Rios-Morales, M., Levels, H., Bruin, S., de Brauw, M., Verheij, J., Kemper, M., Holleboom, A. G., Tushuizen, M. E., Schwartz, T. W., Nielsen, J., Brandjes, D., Dirinck, E., Weyler, J., Verrijken, A., … Nieuwdorp, M. (2022). Microbiome-derived ethanol in nonalcoholic fatty liver disease. *Nature Medicine*, **28**(10), 2100–2106.

Moffett, J. R., Puthillathu, N., Vengilote, R., Jaworski, D. M. & Namboodiri, A M. (2020). Acetate revisited: A key biomolecule at the nexus of metabolism, epigenetics, and oncogenesis – part 2: Acetate and ACSS2 in health and disease. *Frontiers in Physiology*, **11**, 580171.

Montrose, D. C., Nishiguchi, R., Basu, S., Staab, H. A., Zhou, X. K., Wang, H., Meng, L., Johncilla, M., Cubillos-Ruiz, J. R., Morales, D. K., Wells, M. T., Simpson, K. W., Zhang, S., Dogan, B., Jiao, C., Fei, Z., Oka, A., Herzog, J. W., Sartor, R. B. & Dannenberg, A J. (2021). Dietary fructose alters the composition, localization, and metabolism of gut microbiota in association with worsening colitis. *Cellular and Molecular Gastroenterology and Hepatology*, **11**(2), 525–550.

Moreira de Gouveia, M. I., Bernalier-Donadille, A. & Jubelin, G. (2024). Enterobacteriaceae in the human gut: Dynamics and ecological roles in health and disease. *Biology*, **13**(3), 142.

Mueckler, M. & Thorens, B. (2013). The SLC2 (GLUT) family of membrane transporters. *Molecular Aspects of Medicine*, **34**(2–3), 121–138.

Nagai, Y., Nishio, Y., Nakamura, T., Maegawa, H., Kikkawa, R. & Kashiwagi, A. (2002). Amelioration of high fructose-induced metabolic derangements by activation of PPAR$\alpha$. *American Journal of Physiology-Endocrinology and Metabolism*, **282**(5), E1180–E1190.

Nagasue, T., Hirano, A., Torisu, T., Umeno, J., Shibata, H., Moriyama, T., Kawasaki, K., Fujioka, S., Fuyuno, Y., Matsuno, Y., Esaki, M. & Kitazono, T. (2022). The compositional structure of the small intestinal microbial community via balloon-assisted enteroscopy. *Digestion*, **103**(4), 308–318.

Nier, A., Brandt, A., Rajcic, D., Bruns, T. & Bergheim, I. (2019). Short-term isocaloric intake of a fructose- but not glucose-rich diet affects bacterial endotoxin concentrations and markers of metabolic health in normal weight healthy subjects. *Molecular Nutrition & Food Research*, **63**(6), 1800868.

Nogueira, J. P. & Cusi, K. (2024). Role of insulin resistance in the development of nonalcoholic fatty liver disease in people with type 2 diabetes: From bench to patient care. *Diabetes Spectrum*, **37**(1), 20–28.

Oh, J.-H., Alexander, L. M., Pan, M., Schueler, K. L., Keller, M. P., Attie, A. D., Walter, J. &. van Pijkeren, J-P. (2019). Dietary fructose and microbiota-derived short-chain fatty acids promote bacteriophage production in the gut symbiont lactobacillus reuteri. *Cell Host & Microbe*, **25**(2), 273–284.e276.

Oliphant, K. & Allen-Vercoe, E. (2019). Macronutrient metabolism by the human gut microbiome: Major fermentation by-products and their impact on host health. *Microbiome*, **7**(1), 91.

Oren, A. & Garrity, G. M. (2021). Valid publication of the names of forty-two phyla of prokaryotes. *International Journal of Systematic and Evolutionary Microbiology*, **71**(10).

Parker, K., Salas, M. & Nwosu, V. (2011). High fructose corn syrup: Production, uses and public health concerns. *Biotechnology and Molecular Biology Review*, **5**, 71–78.

Patel, C., Douard, V., Yu, S., Tharabenjasin, P., Gao, N. & Ferraris, R. P. (2015). Fructose-induced increases in expression of intestinal fructolytic and gluconeogenic genes are regulated by GLUT5 and KHK. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, **309**(5), R499–R509.

Pessione, E. (2012). Lactic acid bacteria contribution to gut microbiota complexity: Lights and shadows. *Frontiers in Cellular and Infection Microbiology*, **2**.

Prevention CfDCa. National Diabetes Statistics Report (2024).

Rajas, F., Bruni, N., Montano, S., Zitoun, C. & Mithieux, G. (1999). The glucose-6 phosphatase gene is expressed in human and rat small intestine: Regulation of expression in fasted and diabetic rats. *Gastroenterology*, **117**(1), 132–139.

Rezaei Nejad, H., Oliveira, B. C. M., Sadeqi, A., Dehkharghani, A., Kondova, I., Langermans, J. A. M., Guasto, J. S., Tzipori, S., Widmer, G. & Sonkusale, S. R. (2019). Ingestible osmotic pill for in vivo sampling of gut microbiomes. *Advanced Intelligent Systems*, **1**(5), 1900053.

Rinninella, E., Tohumcu, E., Raoul, P., Fiorani, M., Cintoni, M., Mele, M. C., Cammarota, G., Gasbarrini, A. & Ianiro, G. (2023). The role of diet in shaping human gut microbiota. *Best Practice & Research Clinical Gastroenterology*, **62–63**, 101828.

Rogers, N. T., Cummins, S., Jones, C. P., Mytton, O., Rayner, M., Rutter, H., White, M. & Adams, J. (2024). Estimated changes in free sugar consumption one year after the UK soft drinks industry levy came into force: controlled interrupted time series analysis of the National Diet and Nutrition Survey (2011–2019). *Journal of Epidemiology and Community Health*, **78**(9), 578–584. jech-2023-221051.

Rowland, I., Gibson, G., Heinken, A., Scott, K., Swann, J., Thiele, I. & Tuohy, K. (2018). Gut microbiota functions: Metabolism of nutrients and other food components. *European Journal of Nutrition*, **57**(1), 1–24.

Ruigrok, R., Collij, V., Sureda, P., Klaassen, M. A. Y., Bolte, L. A., Jansen, B. H., Voskuil, M. D., Fu, J., Wijmenga, C., Zhernakova, A., Weersma, R. K. & Vich Vila, A. (2021). The composition and metabolic potential of the human small intestinal microbiota within the context of inflammatory bowel disease. *Journal of Crohn's and Colitis*, **15**(8), 1326–1338.

Samuel, V. T., Petersen, K. F. & Shulman, G. I. (2010). Lipid-induced insulin resistance: Unravelling the mechanism. *The Lancet*, **375**(9733), 2267–2277.

Sautin, Y. Y., Nakagawa, T., Zharikov, S. & Johnson, R. J. (2007). Adverse effects of the classic antioxidant uric acid in adipocytes: NADPH oxidase-mediated oxidative/nitrosative stress. *American Journal of Physiology-Cell Physiology*, **293**(2), C584–C596.

Seekatz Anna, M., Schnizlein Matthew, K., Koenigsknecht Mark, J., Baker Jason, R., Hasler William, L., Bleske Barry, E., Young Vincent, B. & Sun, D. (2019). Spatial and temporal analysis of the stomach and small-intestinal microbiota in fasted healthy humans. *mSphere*, **4**(2), e00126–19.

Sellmann, C., Priebs, J., Landmann, M., Degen, C., Engstler, A. J., Jin, C. J., Gärttner, S., Spruss, A., Huber, O. & Bergheim, I. (2015). Diets rich in fructose, fat or fructose and fat alter intestinal barrier function and lead to the development of nonalcoholic fatty liver disease over time. *The Journal of Nutritional Biochemistry*, **26**(11), 1183–1192.

Shalon, D., Culver, R. N., Grembi, J. A., Folz, J., Treit, P. V., Shi, H., Rosenberger, F. A., Dethlefsen, L., Meng, X., Yaffe, E., Aranda-Díaz, A., Geyer, P. E., Mueller-Reif, J. B., Spencer, S., Patterson, A. D., Triadafilopoulos, G., Holmes, S. P., Mann, M., Fiehn, O., … Huang, K. C. (2023). Profiling the human intestinal environment under physiological conditions. *Nature*, **617**(7961), 581–591.

Shu, R., David, E. S. & Ferraris, R. P. (1997). Dietary fructose enhances intestinal fructose transport and GLUT5 expression in weaning rats. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, **272**(3), G446–G453.

Silva, J. C. P., Mota, M., Martins, F. O., Nogueira, C., Gonçalves, T., Carneiro, T., Pinto, J., Duarte, D., Barros, A. S., Jones, J. G. & Gil, A M. (2018). Intestinal microbial and metabolic profiling of mice fed with high-glucose and high-fructose diets. *Journal of Proteome Research*, **17**(8), 2880–2891.

Smith, G. I., Shankaran, M., Yoshino, M., Schweitzer, G. G., Chondronikola, M., Beals, J. W., Okunade, A. L., Patterson, B. W., Nyangau, E., Field, T., Sirlin, C. B., Talukdar, S., Hellerstein, M. K. & Klein, S. (2020). Insulin resistance drives hepatic de novo lipogenesis in nonalcoholic fatty liver disease. *The Journal of Clinical Investigation*, **130**(3), 1453–1460.

Sobajima, T., Yoshimura, S-i, Iwano, T., Kunii, M., Watanabe, M., Atik, N., Mushiake, S., Morii, E., Koyama, Y., Miyoshi, E. & Harada, A. (2014). Rab11a is required for apical protein localisation in the intestine. *Biology Open*, **4**(1), 86–94.

Softic, S., Gupta, M. K., Wang, G.-X., Fujisaka, S., O'Neill, B. T., Rao, T. N., Willoughby, J., Harbison, C., Fitzgerald, K., Ilkayeva, O., Newgard, C. B., Cohen, D. E. & Kahn, C. R. (2017). Divergent effects of glucose and fructose on hepatic lipogenesis and insulin signaling. *The Journal of Clinical Investigation*, **127**(11), 4059–4074.

Softic, S., Stanhope, K. L., Boucher, J., Divanovic, S., Lanaspa, M. A., Johnson, R. J. & Kahn, C R. (2020). Fructose and hepatic insulin resistance. *Critical Reviews in Clinical Laboratory Sciences*, **57**(5), 308–322.

Sokol, H., Pigneur, B., Watterlot, L., Lakhdari, O., Bermúdez-Humarán, L. G., Gratadoux, J.-J., Blugeon, S., Bridonneau, C., Furet, J.-P., Corthier, G., Grangette, C., Vasquez, N., Pochart, P., Trugnan, G., Thomas, G., Blottière, H. M., Doré, J., Marteau, P., Seksik, P. & Langella, P. (2008). Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proceedings of the National Academy of Sciences*, **105**(43), 16731–16736.

Spruss, A., Kanuri, G., Stahl, C., Bischoff, S. C. & Bergheim, I. (2012). Metformin protects against the development of fructose-induced steatosis in mice: Role of the intestinal barrier function. *Laboratory Investigation*, **92**(7), 1020–1032.

Squillario, M., Bonaretti, C., La Valle, A., Di Marco, E., Piccolo, G., Minuto, N., Patti, G., Napoli, F., Bassi, M., Maghnie, M., d'Annunzio, G. & Biassoni, R. (2023). Gut-microbiota in children and adolescents with obesity: Inferred functional analysis and machine-learning algorithms to classify microorganisms. *Scientific Reports*, **13**(1), 11294.

Stanhope, K. L., Schwarz, J. M., Keim, N. L., Griffen, S. C., Bremer, A. A., Graham, J. L., Hatcher, B., Cox, C. L., Dyachenko, A., Zhang, W., McGahan, J. P., Seibert, A., Krauss, R. M., Chiu, S., Schaefer, E. J., Ai, M., Otokozawa, S., Nakajima, K., Nakano, T., … Havel, P. J. (2009). Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *The Journal of Clinical Investigation*, **119**(5), 1322–1334.

Stanislawski, M. A., Dabelea, D., Lange, L. A., Wagner, B. D. & Lozupone, C A. (2019). Gut microbiota phenotypes of obesity. *npj Biofilms and Microbiomes*, **5**(1), 18.

Stearns, J. C., Zulyniak, M. A., De Souza, R. J., Campbell, N. C., Fontes, M., Shaikh, M., Sears, M. R., Becker, A. B., Mandhane, P. J., Subbarao, P., Turvey, S. E., Gupta, M., Beyene, J., Surette, M. G., Anand, S. S. (2017). Ethnic and diet-related differences in the healthy infant microbiome. *Genome Medicine*, **9**(1), 32.

Sumlu, E., Bostancı, A., Sadi, G., Alçığır, M. E. & Akar, F. (2022). Lactobacillus plantarum improves lipogenesis and IRS-1/AKT/eNOS signalling pathway in the liver of high-fructose-fed rats. *Archives of Physiology and Biochemistry*, **128**(3), 786–794.

Sun, S. Z. & Empie, M. W. (2012). Fructose metabolism in humans – what isotopic tracer studies tell us. *Nutrition & Metabolism*, **9**(1), 89.

Szabó, J., Maróti, G., Solymosi, N., Andrásofszky, E., Tuboly, T., Bersényi, A., Bruckner, G. & Hullár, I. (2021). Fructose, glucose and fat interrelationships with metabolic pathway regulation and effects on the gut microbiota. *Acta Veterinaria Hungarica*, **69**(2), 134–156.

Tan, R., Dong, H., Chen, Z., Jin, M., Yin, J., Li, H., Shi, D., Shao, Y., Wang, H., Chen, T., Yang, D. & Li, J. (2021). Intestinal microbiota mediates high-fructose and high-fat diets to induce chronic intestinal inflammation. *Frontiers in Cellular and Infection Microbiology*, **11**, 654074.

Tang, Q., Jin, G., Wang, G., Liu, T., Liu, X., Wang, B. & Cao, H. (2020). Current sampling methods for gut microbiota: A call for more precise devices. *Frontiers in Cellular and Infection Microbiology*, **10**, 00151.

Tappy, L. (2021). Metabolism of sugars: A window to the regulation of glucose and lipid homeostasis by splanchnic organs. *Clinical Nutrition*, **40**(4), 1691–1698.

Tappy, L. & Lê, K.-A. (2010). Metabolic effects of fructose and the worldwide increase in obesity. *Physiological Reviews*, **90**(1), 23–46.

Ter Horst, K. W., Schene, M. R., Holman, R., Romijn, J. A., Serlie, M. J. (2016). Effect of fructose consumption on insulin sensitivity in nondiabetic subjects: A systematic review and meta-analysis of diet-intervention trials12. *The American Journal of Clinical Nutrition*, **104**(6), 1562–1576.

Thompson, F. E., McNeel, T. S., Dowling, E. C., Midthune, D., Morrissette, M. & Zeruto, C. A. (2009). Interrelationships of added sugars intake, socioeconomic status, and race/ethnicity in adults in the United States: National health interview survey, 2005. *Journal of the American Dietetic Association*, **109**(8), 1376–1383.

Uldry, M., Ibberson, M., Hosokawa, M. & Thorens, B. (2002). GLUT2 is a high affinity glucosamine transporter. *Federation of European Biochemical Societies Letters*, **524**(1–3), 199–203.

Utzschneider, K. M. & Kahn, S. E. (2006). The role of insulin resistance in nonalcoholic fatty liver disease. *The Journal of Clinical Endocrinology & Metabolism*, **91**, 4753–4761.

Uyeda, K. & Repa, J. J. (2006). Carbohydrate response element binding protein, ChREBP, a transcription factor coupling hepatic glucose utilization and lipid synthesis. *Cell Metabolism*, **4**(2), 107–110.

van den Berghe, G., Bronfman, M., Vanneste, R. & Hers, H. G. (1977). The mechanism of adenosine triphosphate depletion in the liver after a load of fructose. A kinetic study of liver adenylate deaminase. *Biochemical Journal*, **162**(3), 601–609.

Volynets, V., Louis, S., Pretz, D., Lang, L., Ostaff, M. J., Wehkamp, J. & Bischoff, S. C. (2017). Intestinal barrier function and the gut microbiome are differentially affected in mice fed a western-style diet or drinking water supplemented with fructose. *The Journal of Nutrition*, **147**(5), 770–780.

Vos, M. B., Kimmons, J. E., Gillespie, C., Welsh, J. & Blanck, H. M. (2008). Dietary fructose consumption among US children and adults: The Third National Health and Nutrition Examination Survey. *Medscape Journal of Medicine*, **10**(7), 160.

Waimin, J. F., Nejati, S., Jiang, H., Qiu, J., Wang, J., Verma, M. S. & Rahimi, R. (2020). Smart capsule for non-invasive sampling and studying of the gastrointestinal microbiome. *The Royal Society of Chemistry's Advances*, **10**(28), 16313–16322.

Wang, Y., Qi, W., Song, G., Pang, S., Peng, Z., Li, Y. &. Wang, P. (2020). High-fructose diet increases inflammatory cytokines and alters gut microbiota composition in rats. *Mediators of Inflammation*, **2020**, 6672636.

Wang, Y., Wu, J., Lv, M., Shao, Z., Hungwe, M., Wang, J., Bai, X., Xie, J., Wang, Y. & Geng, W. (2021). Metabolism characteristics of lactic acid bacteria and the expanding applications in food industry. *Frontiers in Bioengineering and Biotechnology*, **9**, 612285.

Ward, B. (2015). Chapter 11-Bacterial Energy Metabolism. In *Molecular Medical Microbiology* (Second Edition), ed. Y.-W. Tang, M. Sussman, D. Liu, I. Poxton & J. Schwartzman, pp. 201–233. Academic Press.

Wei, Y. & Pagliassotti, M. J. (2004). Hepatospecific effects of fructose on c-jun NH2-terminal kinase: Implications for hepatic insulin resistance. *American Journal of Physiology-Endocrinology and Metabolism*, **287**(5), E926–E933.

Wei, Y., Wang, D. & Pagliassotti, M. J. (2005). Fructose selectively modulates c-jun N-terminal kinase activity and insulin signaling in rat primary hepatocytes. *The Journal of Nutrition*, **135**(7), 1642–1646.

White, J. (2014). Sucrose, HFCS, and fructose: History, manufacture, composition, applications, and production. In *Fructose, High Fructose Corn Syrup, Sucrose and Health. Nutrition and Health*, ed. J. Rippe, pp. 13–33. Humana Press.

WHO (2015). *Guideline: Sugars intake for adults and children*. World Health Organization.

WHO (2021). *Global health estimates: Life expectancy and leading causes of death and disability*. World Health Organization.

Wolfe, A. J. (2015). Glycolysis for microbiome generation. *Microbiology Spectrum*, **3**(3). 2014.

Wright, E. M., Loo, D. D. F. & Hirayama, B A. (2011). Biology of human sodium glucose transporters. *Physiological Reviews*, **91**(2), 733–794.

Wu, G. D., Chen, J., Hoffmann, C., Bittinger, K., Chen, Y.-Y., Keilbaugh, S. A., Bewtra, M., Knights, D., Walters, W. A., Knight, R., Sinha, R., Gilroy, E., Gupta, K., Baldassano, R., Nessel, L., Li, H., Bushman, F. D. & Lewis, J. D. (2011). Linking long-term dietary patterns with gut microbial enterotypes. *Science*, **334**(6052), 105–108.

Xie, D., Zhao, H., Lu, J., He, F., Liu, W., Yu, W., Wang, Q., Hisatome, I., Yamamoto, T., Koyama, H. & Cheng, J. (2021). High uric acid induces liver fat accumulation via ROS/JNK/AP-1 signaling. *American Journal of Physiology-Endocrinology and Metabolism*, **320**(6), E1032–E1043.

Xue, G., Feng, J., Zhang, R., Du, B., Sun, Y., Liu, S., Yan, C., Liu, X., Du, S., Feng, Y., Cui, J., Gan, L., Zhao, H., Fan, Z., Cui, X., Xu, Z., Fu, T., Li, C., Huang, L., … Yuan, J. (2023). Three Klebsiella species as potential pathobionts generating endogenous ethanol in a clinical cohort of patients with auto-brewery syndrome: A case control study. *eBioMedicine*, **91**, 104560.

Yersin, S. & Vonaesch, P. (2024). Small intestinal microbiota: From taxonomic composition to metabolism. *Trends in Microbiology*, **32**(10), 970–983.

Yilmaz, B., Fuhrer, T., Morgenthaler, D., Krupka, N., Wang, D., Spari, D., Candinas, D., Misselwitz, B., Beldi, G., Sauer, U. & Macpherson, A J. (2022). Plasticity of the adult human small intestinal stoma microbiota. *Cell Host & Microbe*, **30**, 1773–1787.e1776.

You, M. & Arteel, G. E. (2019). Effect of ethanol on lipid metabolism. *Journal of Hepatology*, **70**(2), 237–248.

Yu, J., Liu, T., Guo, Q., Wang, Z., Chen, Y. &. Dong, Y. (2023). Disruption of the intestinal mucosal barrier induced by high fructose and restraint stress is regulated by the intestinal microbiota and microbiota metabolites. *Microbiology Spectrum*, **11**(2), e04698–04622.

Yuan, J., Chen, C., Cui, J., Lu, J., Yan, C., Wei, X., Zhao, X., Li, N., Li, S., Xue, G., Cheng, W., Li, B., Li, H., Lin, W., Tian, C., Zhao, J., Han, J., An, D., Zhang, Q., … Liu, D. (2019). Fatty liver disease caused by high-alcohol-producing klebsiella pneumoniae. *Cell Metabolism*, **30**(4), 675–688.e7.

Zhao, S., Jang, C., Liu, J., Uehara, K., Gilbert, M., Izzo, L., Zeng, X., Trefely, S., Fernandez, S., Carrer, A., Miller, K. D., Schug, Z. T., Snyder, N. W., Gade, T. P., Titchenell, P. M., Rabinowitz, J. D. & Wellen, K. E. (2020a). Dietary fructose feeds hepatic lipogenesis via microbiota-derived acetate. *Nature*, **579**(7800), 586–591.

Zhao, Z., Chen, L., Zhao, Y., Wang, C., Duan, C., Yang, G., Niu, C. & Li, S. (2020b). Lactobacillus plantarum NA136 ameliorates nonalcoholic fatty liver disease by modulating gut microbiota, improving intestinal barrier integrity, and attenuating inflammation. *Applied Microbiology and Biotechnology*, **104**(12), 5273–5282.

Zhou, X., Zhang, X., Niu, D., Zhang, S., Wang, H., Zhang, X., Nan, F., Jiang, S. & Wang, B. (2023). Gut microbiota induces hepatic steatosis by modulating the T cells balance in high fructose diet mice. *Scientific Reports*, **13**(1), 6701.

Zhu, L., Baker, S. S., Gill, C., Liu, W., Alkhouri, R., Baker, R. D. & Gill, S. R. (2013). Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: a connection between endogenous alcohol and NASH. *Hepatology (Baltimore, Md)*, **57**(2), 601–609.

Zilberstein, B., Quintanilha, A. G., Santos, M. A. A., Pajecki, D., Moura, E. G., Alves, P. R. A., Filho, F. M., de Souza, J. A. U., Gama-Rodrigues, J. (2007). Digestive tract microbiota in healthy volunteers. *Clinics*, **62**(1), 47–56.

Zoetendal, E. G., Raes, J., van den Bogert, B., Arumugam, M., Booijink, C., Troost, F. J., Bork, P., Wels, M., de Vos, W. M. & Kleerebezem, M. (2012). The human small intestinal microbiota is driven by rapid uptake and conversion of simple carbohydrates. *The International Society for Microbial Ecology Journal*, **6**(7), 1415–1426.

## Additional information

### Competing interests

M.N. is co-founder and member of the Scientific Advisory Board of Caelus Pharmaceuticals and Advanced Microbiota Therapeutics, the Netherlands. None of these are directly relevant to the current paper. There are no patents, products in development or marketed products to declare. The other authors declare no conflict of interest.

### Author contributions

F.H.M.W., I.A., M.R-M. and M.N. conceptualized the project and wrote the review. F.H.M.W. created the figures. All authors read and approved the final version of the manuscript.

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### Keywords

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## Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

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